

# Synthesis and *In Vitro* Evaluation of Oxindole Derivatives as Potential Radioligands for 5-HT<sub>7</sub> Receptor Imaging with PET

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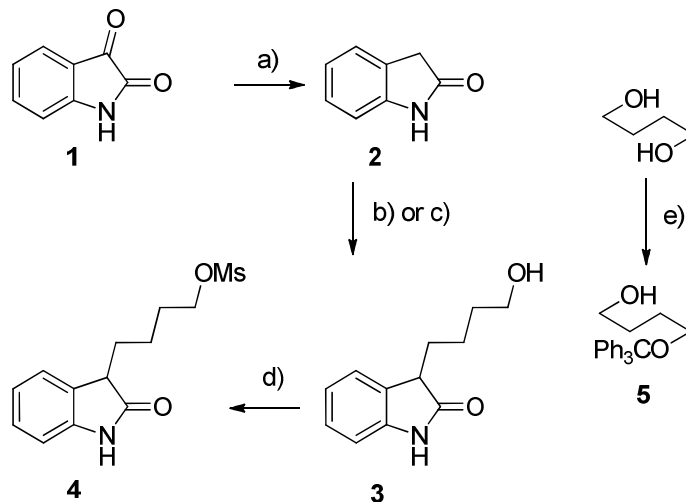
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## Experimental Section

**General.** Chemicals were purchased from Acros, Fluka, Sigma, Tocris, ABX or Merck. Unless otherwise stated, all chemicals were used without further purification. Flash chromatography was performed on silica gel 60 (35-70  $\mu\text{m}$ ). Microwave-assisted syntheses were carried out in a Biotage Initiator apparatus operating in single mode; the microwave cavity producing controlled irradiation at 2.45 GHz (BiotageAB, Uppsala, Sweden). The reactions were run in sealed vials (0.5–2.0 mL). These experiments were performed by employing magnetic stirring and a fixed hold time using variable power to reach it (over a period of 1-2 min) and then maintaining the desired temperature in the vessel for the programmed time period. The temperature was monitored by an IR sensor focused on a point on the reactor vial glass. The IR sensor was calibrated to internal solution reaction temperature by the manufacturer. Thin layer chromatography (TLC) was performed using plates from Merck (silica gel 60 F<sub>254</sub> and aluminium oxide 60 F<sub>254</sub>). <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded using a Bruker AC 300 spectrometer. Chemical shifts are quoted as  $\delta$  values (ppm) downfield from tetramethylsilane (TMS) internal standard. Infrared spectroscopy was performed on a Perkin Elmer FT-IR Spektrometer (Spectrum One). Melting points were determined on a Stanford Research Systems Optimelt system. GC-MS measurements were performed on a Shimadzu apparatus (GCMS-QP 5050). LC-MS tests were performed on 6410 Triple Quad LC/MS instrument. Field desorption mass spectra (FD-MS) were recorded using a Finnigan MAT90 spectrometer and electrospray ionization mass spectrometry (ESI-MS) were performed on a ThermoQuest Navigator Instrument. Analytical high performance liquid chromatography (HPLC) measurements were performed on a Dionex system consisting of a P680A pump and a UVD 170U detector. Chemical purity was checked either by HPLC or by GC. Lipophilicities were determined using a Dionex Ultimate 3000 HPLC equipped with a degasser, an autosampler, a column-oven and a UV-detector. High resolution mass spectra (HRMS) were recorded on a Q-TOF Premier (Waters, USA) and Maxis Impact (BrukerDaltonics, Germany) spectrometer. Full spectral data of previously published compounds can be found in the indicated references.

## Organic syntheses



Supplementary Scheme 1: Synthetic route for methanesulfonic acid 4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-butyl ester (**4**)

### 1,3-Dihydro-2*H*-indol-2-one (2-oxindole, **2**)<sup>(1)</sup>

Isatin (1.47 g, 10 mmol) was dissolved in hydrazine hydrate (98%, 10 mL, 32.5 mmol) and refluxed for 15–30 min (130 °C). The reaction mixture was then poured in cold water, extracted with EtOAc and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and recrystallization from hexane/ethyl acetate afforded 2-oxindole (**3**) (0.93 g, 7 mmol, 70%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 9.78 (1H, s), 7.25–6.66 (4H, m), 3.52 (2H, s). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 176.6, 142.8, 127.9, 125.4, 124.5, 122.3, 110.0, 36.4. GC-MS (EI): RT: 7.89 min, m/z: 133.0 [M]. R<sub>f</sub>: 0.71 (EtOAc).

### 3-(4-Hydroxybutyl)-1,3-dihydro-2*H* indol-2-one (**3**)<sup>(2)</sup>

**Method A:** Oxindole (0.133 g, 1.0 mmol), [Cp · IrCl<sub>2</sub>]<sub>2</sub> (0.020 g, 0.025 mmol), KOH (0.011 g, 0.196 mmol), 4-trityloxybutane-1-ol (**1**) (0.966 g, 3.0 mmol) and anhydrous toluene (2 mL) were combined in a glass tube and sealed, purged with nitrogen and heated for 20 min at 110 °C in a microwave reactor. The solvent was removed and the crude product was purified by silica gel flash column chromatography (EtOAc/heptane 1:2) to afford the intermediate 3-(4-trityloxy-butyl)-1,3-dihydro-2*H*-indol-2-one (160 mg, 0.35 mmol, 37%) as a colourless oil, R<sub>f</sub>: 0.35 (EtOAc/heptane 1:2). To this oil (120 mg, 0.26 mmol) THF (15 mL) and 1 M HCl (5 mL, 5 mmol) was added at room temperature. The solution was refluxed for 20 h, and then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (100 mL) and treated with a saturated

aqueous NaHCO<sub>3</sub> solution (40 mL). The aqueous phase was extracted with EtOAc (2×50 mL), and the combined organic phases were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc) resulting in **2** (32 mg, 0.15 mmol, 60% for the second step, 22% for the two steps). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 9.5 (1H, br s), 7.19 (d, 1H, *J* = 7.1 Hz), 7.17 (1H, dt, *J* = 7.7, 0.8 Hz), 6.98 (1H, dt, *J* = 7.5, 0.9 Hz), 6.89 (1H, d, *J* = 7.7 Hz), 3.57 (2H, t, *J* = 6.4 Hz), 3.45 (1H, t, *J* = 5.9 Hz), 2.93 (1H, br s), 2.00–1.93 (2H, m), 1.59–1.52 (2H, m), 1.48–1.35 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 181.0, 141.7, 129.6, 127.7, 123.9, 122.1, 109.8, 62.0, 46.0, 32.4, 30.0, 21.9. R<sub>f</sub>: 0.27 (EtOAc).

**Method B:** A mixture of oxindole (1.33 g, 0.01 mol), butane-1,4-diol (20 mL) and Raney nickel (1.0 g, ca. 0.017 mol) was heated to 200 °C in a microwave oven (Initiator, Biotage, volume 10 mL) with stirring for 3 h. After the reaction was complete, the mixture was diluted with acetone, filtered over celite and the organic layer reduced. Afterwards the excess of alcohol was removed by Kugelrohr distillation and the residue was either purified using silica gel flash column chromatography (EtOAc) or triturated with heptane to yield in a colourless crystalline product (**2**) (1.9 g, 9.26 mmol, 95%). For spectroscopic data, see Method A.

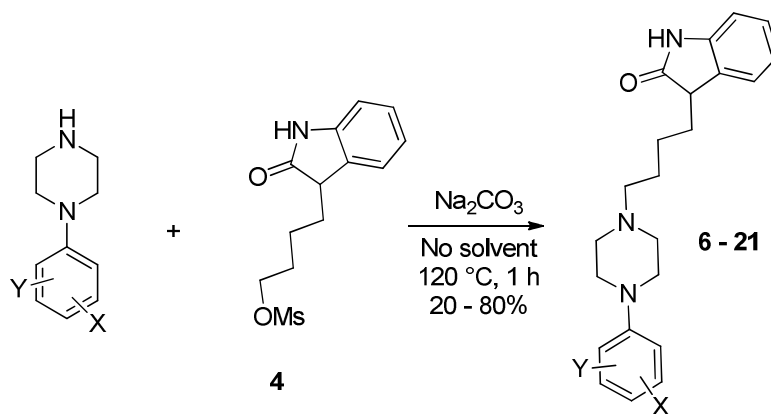
#### **Methanesulfonic acid 4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-butyl ester (**4**)**

**4** was synthesized as described by Volk et al. (2008)<sup>(3)</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 9.33 (1H, s), 7.22 (1H, d, *J* = 7.1 Hz), 7.21 (1H, t, *J* = 7.0 Hz), 7.03 (1H, t, *J* = 7.5 Hz), 6.93 (1H, d, *J* = 7.6 Hz), 4.19 (2H, t, *J* = 6.5 Hz), 3.49 (1H, t, *J* = 6.0 Hz), 2.97 (3H, s), 2.05–1.98 (2H, m), 1.82–1.72 (2H, m), 1.58–1.40 (2H, m). <sup>13</sup>C-NMR (400 MHz, CDCl<sub>3</sub>): δ 180.5, 141.6, 129.1, 127.9, 123.9, 122.3, 109.9, 69.5, 45.7, 37.2, 29.6, 28.9, 21.6. LC-MS (ESI): RT: 2.94 min, *m/z*: 284.1 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.27 (EtOAc)

#### **4-Trityloxybutan-1-ol (**5**)<sup>(4)</sup>**

To a vigorously solution of 1,4-butanediol (27.3 g, 300 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) were added triphenylmethylchloride (8.36 g, 30 mmol) and pyridine (4.83 mL, 60 mmol) at room temperature. After stirring for 90 min, the solution was washed with brine, and the layers were separated. The organic layer was dried over MgSO<sub>4</sub> and the solvents were evaporated in vacuo. The residue was purified by silica gel flash column chromatography (EtOAc/heptane=1:1) to afford 4-trityloxybutan-1-ol (**5**, 7.90 g, 24.9 mmol, 83%) as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ

7.48–7.42 (6H, m), 7.34–7.21 (9H, m), 3.63 (2H, t,  $J = 6.0$  Hz), 3.14 (2H, t,  $J = 6.0$  Hz), 1.76–1.66 (4H, m).  $R_f$ : 0.49 (EtOAc/heptane 1:1)



Supplementary Scheme 2: Synthetic route for **6–21**

**General Procedure to couple 3-[4-(Methanesulfonyloxy)-butyl]oxindole **4** with substituted 4-phenylpiperazines.**

The melt of the secondary amine (12 mmol) was heated to 120 °C under slow stirring. The appropriate 3-[4-(methanesulfonyloxy)-butyl]oxindole (**4**, 12 mmol) and sodium carbonate (1.36 g, 12 mmol) were added. After 1 h reaction time, the brown melt was cooled to ambient temperature. Ethyl acetate and water were added and the layers were separated. The organic layer was dried over  $MgSO_4$  and evaporated. The residual oil or solid was purified by column chromatography using EtOAc as eluent.

**3-[4-(4-Phenylpiperazine-1-yl)butyl]-1,3-dihydro-2H-indol-2-one (**6**)<sup>(5)</sup>**

1-Phenylpiperazine (0.40 g, 2.48 mmol), sodium carbonate (0.26 g, 2.48 mmol) and **4** (0.70 g, 2.48 mmol) yield in **6** (501 mg, 1.44 mmol, 58%) as a colourless solid.  $^1H$ -NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  10.35 (1H, s), 7.24 (1H, d,  $J = 7.3$  Hz), 7.21–7.14 (3H, m), 6.94 (1H, dt,  $J = 1.0, 7.6$  Hz), 6.90 (1H, dd,  $J = 1.0, 7.8$  Hz), 6.82 (1H, d,  $J = 7.7$  Hz), 6.76 (1H, t,  $J = 7.2$  Hz), 3.42 (1H, t,  $J = 4.9$  Hz), 3.07, (4H, t,  $J = 4.9$  Hz), 2.43 (4H, t,  $J = 5.0$  Hz), 2.25 (2H, t,  $J = 7.3$  Hz), 1.91–1.81 (1H, m), 1.82–1.79 (1H, m), 1.43 (2H, quintet,  $J = 7.2$  Hz), 1.31–1.24 (2H, m).

**3-[4-[4-(4-Chlorophenyl)piperazine-1-yl]-butyl]-1,3-dihydro-2H-indol-2-one (**7**)<sup>(3)</sup>**

1-(4-Chlorophenyl)-piperazine (0.844 g, 4.0 mmol), sodium carbonate (0.452 g, 4.0 mmol) and **4** (1.14 g, 4.0 mmol) yield in **7** (1.13 g, 2.87 mmol, 71%) as a white solid. Mp 135–136 °C.  $^1H$ -NMR

(CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.60 (1H, s), 7.24–7.15 (2H, m), 7.18 (2H, d,  $J$  = 9.1 Hz), 7.02 (1H, dt,  $J$  = 0.9, 7.6 Hz), 6.88 (1H, d,  $J$  = 7.7 Hz), 6.81 (2H, d,  $J$  = 9.2 Hz), 3.48 (1H, t,  $J$  = 6.0 Hz), 3.13 (4H, t,  $J$  = 5.0 Hz), 2.55 (4H, t,  $J$  = 5.0 Hz), 2.36 (2H, t,  $J$  = 7.5 Hz), 2.05–1.96 (2H, m), 1.58–1.36 (4H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 101 MHz):  $\delta$  180.3, 149.9, 141.5, 129.7, 128.9, 127.8, 124.4, 124.1, 122.2, 117.1, 109.6, 58.2, 53.0, 49.1, 45.9, 30.3, 26.8, 23.7. LC-MS (ESI): RT: 5.16 min,  $m/z$ : 384.2 [M+H]<sup>+</sup> at 210 and 254 nm.

**3-{4-[4-(4-Fluorophenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (8)<sup>(5)</sup>**

1-(4-Fluorophenyl)piperazine (0.295 g, 1.64 mmol), sodium carbonate (0.180 g, 1.64 mmol) and **4** (0.46 g, 1.64 mmol) yield in **8** (446 mg, 1.18 mmol, 72%) as a colorless oil. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  9.33 (1H, s), 7.21 (1H, t,  $J$  = 6.7 Hz), 7.19 (1H, d,  $J$  = 7.7 Hz), 7.01 (1H, dt,  $J$  = 0.9, 7.5 Hz), 6.94 (2H, t,  $J$  = 8.8 Hz), 6.89 (1H, d,  $J$  = 7.7 Hz), 6.85 (2H, dd,  $J$  = 4.6, 9.2 Hz), 3.37 (1H, t,  $J$  = 5.9 Hz), 3.09 (4H, t,  $J$  = 5.0 Hz), 2.56 (4H, t,  $J$  = 5.0 Hz), 2.36 (2H, t,  $J$  = 7.5 Hz), 2.04–1.95 (2H, m), 1.57–1.36 (4H, m).

**3-{4-[4-(2-Methylphenyl)piperazine-1-yl]-butyl}-1,3-dihydro-2H-indol-2-one (9).**

1-(2-Methylphenyl)piperazine (0.35 g, 1.65 mmol), sodium carbonate (0.37 g, 3.3 mmol) and **4** (0.46 g, 1.65 mmol) yield in **9** (0.436 g, 1.22 mmol, 72%) as an colourless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.00 (1H, s), 7.16–7.11 (2H, m), 7.09 (2H, d,  $J$  = 2.25 Hz), 6.87 (4H, d,  $J$  = 12 Hz), 3.42 (1H, t,  $J$  = 6 Hz), 2.84 (4H, br s), 2.50 (4H, br s), 2.30 (2H, t,  $J$  = 9 Hz), 2.20 (3H, s), 1.97–1.88 (2H, m), 1.55–1.43 (2H, m), 1.41–1.28 (2H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  180.7, 151.6, 141.8, 132.7, 131.2, 129.9, 128.0, 126.7, 124.3, 123.2, 122.4, 119.1, 109.9, 58.6, 53.9, 51.8, 46.2, 30.6, 27.0, 24.0, 18.1. MS (FD)  $m/z$  (% rel. int.): 363.42 (100.0 [M]<sup>+</sup>), 364.44 (56.11 [M+1]<sup>+</sup>), 365.43 (810 [M+2]<sup>+</sup>). LC-MS (ESI): RT: 4.965 min,  $m/z$ : 364.2 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc); HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>O 364.2383, found 364.2390.

**3-{4-[4-(4-Methylphenyl)piperazine-1-yl]-butyl}-1,3-dihydro-2H-indol-2-one (10).**

1-(4-Methylphenyl)piperazine (0.704 g, 3.98 mmol), sodium carbonate (0.452 g, 4.0 mmol) and **4** (1.14 g, 4.0 mmol) yield in **10** (1.09 g, 3.0 mmol, 76%) as a white solid. Mp 109–110 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.98 (1H, s), 7.23–7.17 (2H, m), 7.07–6.99 (3H, m), 6.89–6.80 (3H, m), 3.48 (1H, t,  $J$  = 6.0 Hz), 3.14 (4H, t,  $J$  = 6.0 Hz), 2.58 (4H, t,  $J$  = 6.0 Hz), 2.37 (2H, t,  $J$  = 6.0 Hz), 2.28 (3H, s), 2.04–1.96 (2H, m), 1.61–1.51 (2H, m), 1.49–1.37 (2H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz):

$\delta$  181.0, 149.8, 141.9, 130.1, 130.0, 129.6, 128.5, 122.6, 116.8, 110.0, 58.7, 53.7, 50.0, 46.0, 30.8, 27.2, 24.2, 20.9. MS (FD)  $m/z$  (% rel. int.): 363.41 (100.0  $[M]^+$ ), 364.41 (27.74  $[M+1]^+$ ), 365.44 (3.14  $[M+2]^+$ ). LC-MS (ESI): RT: 4.83 min,  $m/z$ : 364.2  $[M+H]^+$  at 210 and 254 nm.  $R_f$ : 0.2 (EtOAc). HRMS (ESI)  $[MH^+]$  calcd. for  $C_{23}H_{30}N_3O$  364.2383, found 364.2386.

**3-{4-[4-(2-(2-Fluoroethoxy)phenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (11).**

1-(2-(2-Fluoroethoxy)phenyl)piperazine (0.450 g, 2.0 mmol), sodium carbonate (0.226 g, 2.0 mmol) and **4** (0.57 g, 2.0 mmol) yield in **11** (140 mg, 0.34 mmol, 20%) as a colorless oil.  $^1H$ -NMR (300 MHz,  $CDCl_3$ ):  $\delta$  9.23 (1H, s), 7.14–7.07 (2H, m), 6.94–6.74 (6H, m), 4.75 (1H, t,  $J = 2.5$  Hz), 4.59 (1H, t,  $J = 2.5$  Hz), 4.19 (1H, d,  $J = 2.5$  Hz), 4.10 (1H, t,  $J = 2.5$  Hz), 3.38 (1H, t,  $J = 6$  Hz), 3.03 (4H, br s), 2.53 (4H, br s), 2.30 (2H, t,  $J = 6.0$  Hz), 1.98–1.84 (2H, m), 1.53–1.41 (2H, m), 1.40–1.23 (2H, m).  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ ):  $\delta$  181.2, 151.2, 142.4, 142.2, 130.1, 128.2, 124.5, 123.0, 122.6, 122.5, 119.0, 114.0, 110.2, 82.4 (d,  $J = 177$  Hz), 67.9 (d,  $J = 27$  Hz), 67.7, 58.8, 53.9, 50.9, 46.5, 30.8, 27.2, 24.3. MS (FD)  $m/z$  (% rel. int.): 411.42 (100.0  $[M]^+$ ), 412.41 (38.38  $[M+1]^+$ ). LC-MS (ESI): RT: 5.10 min,  $m/z$ : 412.4  $[M+H]^+$  at 210 and 254 nm.  $R_f$ : 0.2 (EtOAc). HRMS (ESI)  $[MH^+]$  calcd. for  $C_{24}H_{31}FN_3O_2$  412.2400, found 412.2410.

**3-{4-[4-(2-(3-Fluoroethoxy)phenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (12).**

1-(2-(3-Fluoroethoxy)phenyl)piperazine (0.37 g, 1.64 mmol), sodium carbonate (0.180 g, 1.64 mmol) and **4** (0.46 g, 1.64 mmol) yield in **12** (193 mg, 0.46 mmol, 27%) as a colorless oil.  $^1H$ -NMR (300 MHz,  $CDCl_3$ ):  $\delta$  9.17 (1H, s), 7.23–7.12 (3H, m), 7.01 (1H, t,  $J = 9$  Hz), 6.89 (1H, d,  $J = 2.3$  Hz), 6.55 (1H, d,  $J = 2.3$  Hz), 6.49 (1H, s), 6.40 (1H, d,  $J = 2.3$  Hz), 4.81 (1H, t,  $J = 3.0$  Hz), 4.65 (1H, t,  $J = 3.0$  Hz), 4.24 (1H, t,  $J = 3.0$  Hz), 4.14 (1H, t,  $J = 3.0$  Hz), 3.48 (1H, t,  $J = 6.0$  Hz), 3.18 (4H, t,  $J = 6.0$  Hz), 2.57 (4H, t,  $J = 6.0$  Hz), 2.37 (2H, t,  $J = 9.0$  Hz), 2.08–1.96 (2H, m), 1.61–1.52 (2H, m), 1.49–1.31 (2H, m).  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ ):  $\delta$  181.1, 159.8, 153.0, 142.2, 130.3, 130.0, 128.2, 124.5, 122.6, 110.2, 109.7, 105.2, 103.4, 82.4 (d,  $J = 170$  Hz), 67.4 (d,  $J = 24$  Hz), 67.3, 58.6, 53.5, 49.2, 46.5, 30.8, 27.1, 24.2. MS (FD)  $m/z$  (% rel. int.): 411.46 (100.0  $[M]^+$ ), 412.47 (34.62  $[M+1]^+$ ), 413.48 (5.22  $[M+2]^+$ ). LC-MS (ESI): RT: 5.09 min,  $m/z$ : 412.4  $[M+H]^+$  at 210 and 254 nm.  $R_f$ : 0.2 (EtOAc). HRMS (ESI)  $[MH^+]$  calcd. for  $C_{24}H_{31}FN_3O_2$  412.2400, found 412.2407.

**3-{4-[4-(2-Methoxyphenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (13).**

1-(2-Methoxyphenyl)piperazine (0.337 g, 1.76 mmol), sodium carbonate (0.198 g, 1.76 mmol) and **4** (0.50 g, 1.76 mmol) yield in **13** (0.621 g, 1.64 mmol, 93%) as an colourless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.90 (1H, s), 7.17–7.08 (2H, m), 6.95–6.74 (6H, m), 3.76 (3H, s), 3.39 (1H, t, *J* = 6.0 Hz), 3.00 (4H, br s), 2.55 (4H, br s), 2.30 (2H, t, *J* = 9.0 Hz), 1.98–1.87 (2H, m), 1.55–1.42 (2H, m), 1.40–1.28 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 180.8, 152.8, 142.1, 141.7, 130.0, 128.0, 124.5, 123.4, 122.4, 121.4, 118.5, 111.6, 110.1, 55.7, 53.8, 50.9, 46.1, 30.8, 27.1, 24.2. MS (FD) *m/z* (% rel. int.): 379.43 (100.0 [M]<sup>+</sup>), 380.42 (29.58 [M+1]<sup>+</sup>). LC-MS (ESI): RT: 4.948 min, *m/z*: 380.2 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub> 380.2338, found 380.2331.

**3-{4-[4-(3-Methoxyphenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (14).**

1-(3-Methoxyphenyl)piperazine (0.674 g, 3.51 mmol), sodium carbonate (0.397 g, 3.51 mmol) and **4** (1 g, 3.51 mmol) yield in **14** (0.417 g, 1.10 mmol, 32%) as a colourless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.25 (1H, s), 7.17–7.04 (3H, m), 6.94 (1H, t, *J* = 9.0 Hz), 6.79 (1H, d, *J* = 9.0 Hz), 6.46–6.42 (1H, m), 6.46–6.31 (2H, m), 3.70 (3H, s), 3.40 (1H, t, *J* = 6.0 Hz), 3.10 (4H, t, *J* = 6.0 Hz), 2.49 (4H, t, *J* = 6.0 Hz), 2.30 (2H, t, *J* = 6.0 Hz), 1.92–1.88 (2H, m), 1.54–1.41 (2H, m), 1.40–1.29 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 180.6, 160.7, 152.8, 141.8, 129.9, 129.8, 128.0, 124.3, 122.4, 109.9, 109.0, 104.6, 102.6, 102.6, 58.4, 55.3, 53.3, 49.1, 46.2, 30.5, 26.9, 23.9. MS (FD) *m/z* (% rel. int.): 379.41 (100.0 [M]<sup>+</sup>), 380.41 (18.26 [M+1]<sup>+</sup>). LC-MS (ESI): RT: 4.990 min, *m/z*: 380.4 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub> 380.2338, found 380.2340.

**3-{4-[4-(2-Hydroxyphenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (15).**

The synthesis of **15** was carried out without any base. 1-[2-(*Tert*-butyl-diphenyl-silanyloxy)-phenyl]piperazine (2.06 g, 4.97 mmol) and **4** (1.40 g, 4.97 mmol) yield in **15** (942 mg, 2.58 mmol, 52%) as a white crystal. Mp 80–83 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 9.45 (1H, br s), 7.26–6.70 (8H, m), 6.19 (1H, br s), 3.88 (1H, t, *J* = 6.0 Hz), 2.81 (4H, t, *J* = 6.0 Hz), 2.62 (4H, br s), 2.30 (2H, t, *J* = 6.0 Hz), 1.97–1.84 (2H, m), 1.52–1.40 (2H, m), 1.38–1.22 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 181.3, 151.7, 142.3, 139.3, 130.1, 128.3, 126.7, 124.5, 122.6, 121.7, 120.4, 114.6, 110.2, 58.5, 54.0, 52.5, 46.5, 30.7, 26.9, 24.3. MS (FD) *m/z* (% rel. int.): 365.42 (50.0 [M]<sup>+</sup>), 366.42



(100.0 [M+1]<sup>+</sup>), 367.38 (12.56 [M+2]<sup>+</sup>). LC-MS (ESI): RT: 4.69 min, m/z: 366.3 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub> 366.2181, found 366.2184.

**3-{4-[4-(3-Hydroxyphenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (16).**

The synthesis of **16** was carried out without any base. 3-(Piperazin-1-yl)phenol (0.63 g, 3.55 mmol) and **4** (1.0 g, 3.55 mmol) yield in **16** (777 mg, 2.13 mmol, 60%) as white crystals. Mp 79–81 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.57 (1H, s), 7.12–7.07 (2H, m), 6.99–6.89 (2H, m), 6.75 (1H, d, *J* = 9.0 Hz), 6.35–6.32 (1H, m), 6.26–6.21 (2H, m), 3.39 (1H, t, *J* = 6.0 Hz), 3.04 (4H, t, *J* = 6.0 Hz), 2.47 (4H, t, *J* = 6.0 Hz), 2.26 (2H, t, *J* = 9.0 Hz), 1.96–1.87 (2H, m), 1.51–1.41 (2H, m), 1.38–1.18 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 180.7, 157.4, 152.3, 141.7, 130.2, 129.9, 128.0, 124.2, 122.8, 109.6, 108.5, 106.5, 103.9, 59.1, 53.3, 48.7, 46.0, 30.3, 26.7, 23.9. MS (FD) m/z (% rel. int.): 365.41 (100.0 [M]<sup>+</sup>), 366.41 (72.26 [M+1]<sup>+</sup>), 367.40 (16.90 [M+2]<sup>+</sup>). LC-MS (ESI): RT: 4.29 min, m/z: 366.3 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub> 366.2181, found 366.2175.

**3-{4-[4-(4-Hydroxyphenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (17).**

The synthesis of **17** was carried out without any base. 4-(Piperazin-1-yl)phenol (0.63 g, 3.55 mmol) and **4** (1.0 g, 3.55 mmol) yield in **17** (440 mg, 1.2 mmol, 34%) as white crystals. Mp 83–85 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.23 (1H, br s), 7.19 (2H, m), 7.01 (1H, m), 7.89–6.70 (5H, m), 3.46 (1H, t, *J* = 6.0 Hz), 3.04 (4H, br s), 2.58 (4H, br s), 2.36 (2H, t, *J* = 6.0 Hz), 2.05–1.91 (2H, m), 1.61–1.49 (2H, m), 1.44–1.35 (2H, m). LC-MS (ESI): RT: 2.12 min, m/z: 366.3 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.1 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub> 366.2181, found 366.2188.

**3-{4-[4-(2-(Methylthio)phenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (18).**

1-(2-(Methylthio)phenyl)piperazine (0.34 g, 1.64 mmol), sodium carbonate (0.180 g, 1.64 mmol), and **4** (0.46 g, 1.64 mmol) yield in **18** (421 mg, 1.07 mmol, 64%) as a colorless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 9.78 (1H, s), 7.25–7.14 (2H, m), 7.09–6.96 (5H, m), 6.86 (1H, d, *J* = 6.0 Hz), 3.46 (1H, t, *J* = 6.0 Hz), 3.00 (4H, br s), 2.59 (4H, br s), 2.44–2.31 (5H, m), 2.05–1.91 (2H, m), 1.64–1.49 (2H, m), 1.48–1.30 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 181.4, 149.8, 142.4, 135.3, 130.2, 128.2, 125.3, 124.8, 122.6, 124.4, 122.5, 120.1, 110.3, 58.9, 53.9, 51.7, 46.7, 30.8, 27.2, 24.2, 14.7. LC-MS (ESI): RT: 2.65 min, m/z: 396.3 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.2 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>OS 396.2110, found 380.2115.

**3-{4-[4-(2-(Dimethylamino)phenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (19).**

*N,N*-Dimethyl-2-(piperazin-1-yl)aniline (0.855 g, 3.08 mmol), sodium carbonate (0.348 g, 3.08 mmol) and **4** (525 mg, 2.9 mmol) yield in **19** (999 mg, 2.55 mmol, 83%) as a colourless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 9.06 (1H, s), 7.16–7.09 (2H, m), 6.95–6.91 (1H, m), 6.86–6.77 (5H, m), 3.40 (1H, t, *J* = 6.0 Hz), 3.05 (4H, br s), 2.72 (6H, s), 2.50 (4H, br s), 2.29 (2H, t, *J* = 6.0 Hz), 1.97–1.89 (2H, m), 1.56–1.41 (2H, m), 1.40–1.22 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 180.2, 145.7, 144.2, 142.0, 129.9, 128.0, 124.3, 122.6, 122.4, 121.9, 118.4, 118.1, 110.0, 54.1, 49.1, 46.3, 41.9, 30.6, 27.0, 24.0. LC-MS (ESI): RT: 1.8 min; *m/z*: 393.33 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.2 (EtOAc). HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>24</sub>H<sub>33</sub>N<sub>4</sub>O 393.2654, found 393.2652.

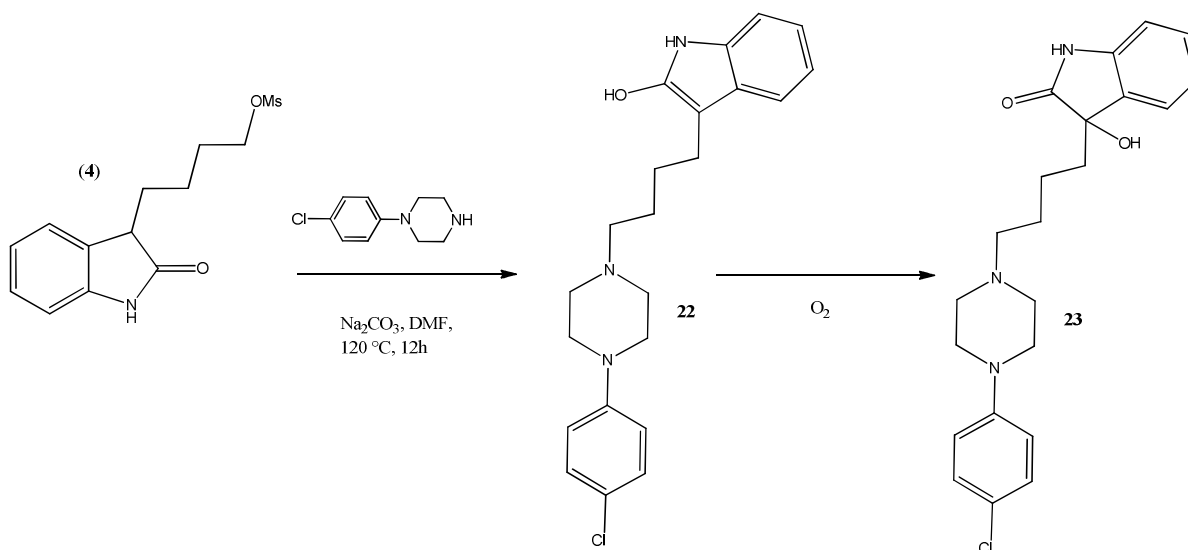
**3-{4-[4-(2-Cyanophenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (20).**

1-(2-Cyanophenyl)piperazine (0.93 g, 5.0 mmol), sodium carbonate (0.52 g, 5.0 mmol) and **4** (1.41 g, 5.0 mmol) yield in **20** (1.37 g, 3.65 mmol, 73%) as a colourless solid. Mp 130–134 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 8.09 (1H, s), 7.58 (1H, dd, *J*<sub>1</sub> = 3 Hz, *J*<sub>2</sub> = 6 Hz), 7.52–7.47 (1H, m), 7.27–7.22 (2H, m), 7.08–7.00 (3H, m), 6.91 (1H, d, *J* = 3.0 Hz), 3.53–3.48 (1H, m), 3.26 (4H, t, *J* = 3.0 Hz), 2.67 (4H, t, *J* = 6.0 Hz), 2.44 (2H, t, *J* = 3.0 Hz), 2.08–1.98 (2H, m), 1.63–1.38 (4H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 179.9, 155.7, 141.4, 134.3, 133.8, 129.7, 127.9, 124.2, 122.3, 121.7, 118.6, 118.5, 109.5, 105.6, 58.1, 53.1, 41.4, 45.9, 30.4, 26.7, 23.7. LC-MS (ESI): RT: 4.94 min; *m/z*: 375.2 [M+H]<sup>+</sup> at 210 and 254 nm. HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>23</sub>H<sub>27</sub>N<sub>4</sub>O 375.2185, found 375.2191.

**3-{4-[4-(4-Fluoro-3-nitrophenyl)piperazine-1-yl]butyl}-1,3-dihydro-2H-indol-2-one (21).**

**21** was purified by column chromatography using EtOAc/heptane/Et<sub>3</sub>N (2.5: 2.5:0.5). 1-(4-Fluoro-3-nitrophenyl)piperazine (1.023 g, 2.48 mmol), sodium carbonate (0.26 g, 2.48 mmol) and **4** (0.7 g, 2.48 mmol) yield in **21** (796 mg, 1.93 mmol, 78%) as a colourless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.47 (1H, s), 7.39–7.36 (1H, m), 7.18–7.09 (2H, m), 7.16–6.99 (2H, m), 6.97–6.92 (1H, m), 6.81 (1H, d, *J* = 0.75 Hz), 3.41 (1H, t, *J* = 6.0 Hz), 3.10 (4H, t, *J* = 6.0 Hz), 2.49 (4H, t, *J* = 6.0 Hz), 2.30 (2H, t, *J* = 6.0 Hz), 1.96–1.89 (2H, m), 1.53–1.41 (2H, m), 1.39–1.25 (2H, m). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 181.1, 149.0 (d, *J* = 255 Hz), 147.9, 142.0, 137.3 (d, *J* = 9.0 Hz), 129.8, 128.0, 124.2, 122.6 (d, *J* = 8.3 Hz), 122.3, 118.7 (d, *J* = 21 Hz), 112.0, 110.0, 58.2, 52.9, 48.9, 46.3, 30.4, 26.8, 23.8. LC-MS (ESI): RT: 2.3 min; *m/z*: 413.3 [M+H]<sup>+</sup> at 210 and 254 nm. R<sub>f</sub>: 0.25

(EtOAc/heptane/Et<sub>3</sub>N 2.5:2.5:0.5); HRMS (ESI) [MH<sup>+</sup>] calcd. for C<sub>22</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>3</sub> 413.1989, found 413.1997.



Supplementary Scheme 3: Synthesis route for **23**

### **Comment:**

Interestingly, treatment of various arylpiperazines using DMF and Na<sub>2</sub>CO<sub>3</sub> did not lead to the desired products. <sup>1</sup>H-NMR data revealed that the hydrogen atom in C(3) position was missing [compound **22**], whereas LC-MS spectroscopy showed the right value. We believe that DMF is stabilizing the enol-form similar to the tautomerism of azaoxindoles described by Finch et al. (6). Nevertheless, the resulting product was tried to selectively C(3)-alkylated using 1,2-bromofluoroethane and 2 equivalents of *n*-BuLi. Surprisingly, the purified compound **23** bore a hydroxyl moiety in position C(3) instead of a fluoroethyl group. We believe that this unexpected outcome may be explained by the occurrence of long-lived radicals formed from DMF in the presence of small amounts of bases (7). These radicals may lead to a rapid autooxidation resulting in the hydroxyl compound. A similar behavior was described by Nakagawa et al. (8).

### **3-(4-(4-(4-Chlorophenyl)piperazine-1-yl)butyl)-3-hydroxyindolin-2-one (**23**).**

(4-Chlorophenyl)-piperazine (0.844 g, 4.0 mmol), sodium carbonate (0.452 g, 4.0 mmol) and **4** (1.14 g, 4.0 mmol) were dissolved in 50 mL of dry DMF and heated to 120 °C. After 1 h reaction time, the crude mixture was concentrated, dissolved in ethyl acetate and water, and finally extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub> and evaporated. The residual oil or solid was



***Tert*-butyl 4-(2-hydroxyphenyl)piperazine-1-carboxylate (24).**

*N*-2-hydroxyphenylpiperazine (2.8 g, 15.7 mmol), NaHCO<sub>3</sub> (2.3 g, 27 mmol), Boc<sub>2</sub>O (4.1 g, 18.8 mmol) yield in **24** (2.43 g, 8.9 mmol, 57%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13–7.05 (2H, m), 6.95–6.92 (1H, m), 6.87–6.19 (1H, m), 3.59–3.56 (4H, t, *J* = 6.0 Hz), 2.83–2.80 (4H, t, *J* = 6.0 Hz), 1.47 (9H, s). MS (FD) *m/z* (% rel. int.): 278.2 (100.0 [M]<sup>+</sup>), 279.2 (17.27[M+1]<sup>+</sup>). R<sub>f</sub>: 0.6 (PE/EtOAc 7:3).

***Tert*-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (25).**

*N*-3-hydroxyphenylpiperazine (5.0 g, 28.04 mmol), NaHCO<sub>3</sub> (4.11 g, 48.0 mmol), Boc<sub>2</sub>O (7.32 g, 33.6 mmol) yield in **25** (6.98 g, 25.05 mmol, 89%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.12–7.07 (1H, t, *J* = 6.0 Hz), 6.52–6.40 (3H, m), 3.60–3.57 (4H, t, *J* = 6.0 Hz), 3.12–3.08 (4H, t, *J* = 6.0 Hz), 1.46 (9H, s). MS (FD) *m/z* (% rel. int.): 278.1 (100.0 [M]<sup>+</sup>), 279.1 (10.78 [M+1]<sup>+</sup>). R<sub>f</sub>: 0.52 (PE/EtOAc 7:3).

***Tert*-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate (26).**

*N*-4-Hydroxyphenylpiperazine (2.8 g, 15.7 mmol), NaHCO<sub>3</sub> (2.3 g, 27.0 mmol), Boc<sub>2</sub>O (4.1 g, 18.8 mmol) yield in **31** (4.01 g, 14.4 mmol, 92%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.10–6.78 (4H, m), 3.70–3.66 (4H, t, *J* = 6.0 Hz), 3.11–3.05 (4H, t, *J* = 6.0 Hz), 1.46 (9H, s). MS (FD) *m/z* (% rel. int.): 278.1 (100.0 [M]<sup>+</sup>), 279.1 (15.56 [M+1]<sup>+</sup>). R<sub>f</sub>: 0.35 (PE/EtOAc 7:3).

**General Wilkinson Ether Synthesis Procedure with 1,2-Bromofluoroethane.<sup>(9)</sup>**

NaH (7.19 mmol) was gradually added to the corresponding phenolic derivatives (7.19 mmol) dissolved in 50 mL of dry, cold DMF (0 °C) and stirred for 30 min. To the resulting mixture 1,2-bromofluoroethane (7.19 mol) was slowly added and stirred for 20 h at 60 °C. After evaporation of the solvent, the residue was taken up in EtOAc, washed with water and finally extracted with EtOAc (3×70 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. Chromatography of the residue gave the pure product.

***Tert*-butyl 4-(2-(2-fluoroethoxy)phenyl)piperazine-1-carboxylate (27a).**

*Tert*-butyl 4-(2-hydroxyphenyl)piperazine-1-carboxylate (2.0 g, 7.19 mmol), NaH (189.4 mg, 7.19 mmol), 1,2-bromofluoroethane (916 mg, 0.52 mL; 7.19 mmol) yield in **27a** (2.04 g, 5.8 mmol, 86%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.96–6.84 (4H, m), 4.85–4.82 (1H, m), 4.69–4.66 (1H, m),

4.30–4.27 (1H, m), 4.20–4.18 (1H, m), 3.59 (4H, br s), 3.02 (4H, br s), 1.45 (9H, s). MS (FD) *m/z* (% rel. int.): 324.2 (100.0 [M]<sup>+</sup>), 325.2 (11.16 [M+1]<sup>+</sup>). R<sub>f</sub>: 0.54 (PE/EtOAc 7:3).

***Tert*-butyl 4-(2-(3-fluoroethoxy)phenyl)piperazine-1-carboxylate (28b).**

*Tert*-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (2.0 g, 7.19 mmol), NaH (189.4 mg, 7.19 mmol), 1,2-bromofluoroethane (916 mg, 0.52 mL, 7.19 mmol) yield in **28b** (1.92 g, 5.5 mmol, 81%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.18–7.13 (1H, m), 6.56–6.40 (3H, m), 4.81–4.78 (1H, m), 4.65–4.63 (1H, m), 4.24–4.21 (1H, m), 4.14–4.11 (1H, m), 3.56–3.52 (4H, t, *J* = 6.0 Hz), 3.12–3.09 (4H, t, *J* = 6.0 Hz), 1.46 (9H, s). MS (FD) *m/z* (% rel. int.): 323.9 (100.0 [M]<sup>+</sup>), 324.9 (17.82 [M+1]<sup>+</sup>). R<sub>f</sub>: 0.7 (PE/EtOAc 7:3).

***Tert*-butyl 4-(2-(4-fluoroethoxy)phenyl)piperazine-1-carboxylate (29c).**

*Tert*-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate (2.0 g, 7.19 mmol), NaH (189.4 mg, 7.19 mmol), 1,2-bromofluoroethane (916 mg, 0.52 mL, 7.19 mmol) yield in **29c** (1.55 g, 4.79 mmol, 67%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.94–6.81 (4H, m), 4.80–4.77 (1H, m), 4.64–4.61 (1H, m), 4.21–4.18 (1H, m), 4.11–4.08 (1H, m), 3.57–3.54 (4H, t, *J* = 6.0 Hz), 3.01–2.97 (4H, t, *J* = 6.0 Hz), 1.46 (9H, s). MS (FD) *m/z* (% rel. int.): 323.9 (100.0 [M]<sup>+</sup>), 324.9 (17.23 [M+1]<sup>+</sup>); R<sub>f</sub>: 0.76 (PE/EtOAc 7:3).

**General Boc-Deprotection Procedure.<sup>(9)</sup>**

The starting material (1.0 g, 2.4 mmol) was carefully and gradually dissolved in trifluoroacetic acid (TFA, 10 mL). After stirring for 2 h at room temperature, the solution was diluted with ether (30 mL) and carefully neutralized with NH<sub>4</sub>OH and ice bath cooling. The layers were separated and the aqueous layer was extracted with ether (3×50 mL). The combined organic extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to afford a viscous oil. Silica gel column chromatography of the residue gave the pure products.

**1-(2-(2-Fluoroethoxy)phenyl)piperazine (27).<sup>(9)</sup>**

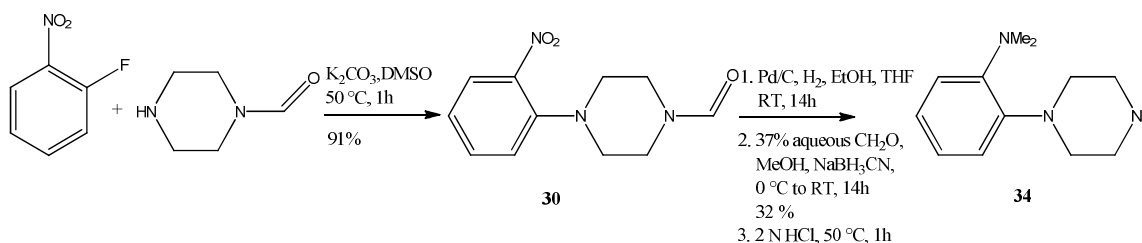
Yield: 435 mg (1.55 mmol, 64%) of **27** as a white solid. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.07–6.85 (4H, m), 4.86–4.81 (1H, m), 4.70–4.66 (1H, m), 4.31–4.24 (1H, m), 4.23–4.14 (1H, m), 3.37 (8H, br s). MS (FD) *m/z* (% rel. int.): 223.5 (100.0 [M]<sup>+</sup>), 224.5 (13.32 [M+1]<sup>+</sup>). R<sub>f</sub>: 0.92 (CH<sub>3</sub>Cl/MeOH 8:1). For more spectroscopic data see <sup>(9)</sup>.

### 1-(2-(3-Fluoroethoxy)phenyl)piperazine (28).<sup>(9)</sup>

Yield: 653 mg (2.31 mmol, 95%) as a white solid. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.18–7.12 (1H, m), 6.65–6.35 (3H, m), 4.81–4.78 (1H, m), 4.65–4.62 (1H, m), 4.23–4.17 (1H, m), 4.14–4.11 (1H, m), 3.34 (1H, br s), 3.18–3.14 (4H, m), 3.06–3.02 (4H, m). MS (FD) m/z (% rel. int.): 223.6 (100.0 [M]<sup>+</sup>), 224.6 (10.02 [M+1]<sup>+</sup>). For more spectroscopic data see <sup>(9)</sup>.

### 1-(2-(4-Fluoroethoxy)phenyl)piperazine (29).<sup>(9)</sup>

Yield: 676 mg (2.39 mmol, 99%) as a white solid. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.89–6.83 (4H, m), 4.85–4.73 (1H, m), 4.64–4.61 (1H, m), 4.22–4.16 (1H, m), 4.11–4.08 (1H, m), 3.03 (8H, s), 2.30 (1H, bs); MS (FD) m/z (% rel. int.): 224.1 (100.0 [M]<sup>+</sup>), 225.1 (1.12 [M+1]<sup>+</sup>). For more spectroscopic data see <sup>(9)</sup>.



Supplementary Scheme 5: Synthesis of *N,N*-dimethyl-2-(piperazin-1-yl)aniline (**34**)

### 4-(2-Nitrophenyl)piperazine-1-carbaldehyde (**30**).<sup>(10)</sup>

To a stirred suspension of 1-fluoro-2-nitrobenzene (8.0 g, 57 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.62 g, 62 mmol) in DMSO (40 mL) was added piperazine-1-carbaldehyde (7.12 g, 62.24 mmol, 6.43 mL) at room temperature, and the mixture was stirred at 50 °C for 1 h. After addition of water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to give (12.19 g, 52 mmol, 91%) of the product as an orange solid. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.06 (1H, s), 7.78–7.75 (1H, m), 7.53–7.25 (1H, m), 7.21–7.07 (2H, m), 3.69 (2H, t, *J* = 5.0 Hz), 3.53 (2H, t, *J* = 5.0 Hz), 3.07–3.00 (4H, m).

### 4-(2-Aminophenyl)piperazine-1-carbaldehyde (**32**).<sup>(10)</sup>

**30** (10.0 g, 42.5 mmol) in EtOH (100 mL) and THF (100 mL) was hydrogenated over 10% Pd/C (2.5 g) under an atmospheric pressure of H<sub>2</sub> for 14 h at room temperature. The mixture was filtered, and the filtrate was concentrated to give 4-(2-aminophenyl)piperazin-1-carbaldehyde (8.71 g, 42.5 mmol) as white crystals, which were used in the next reaction without further purification. <sup>1</sup>H-NMR

(300 MHz, CDCl<sub>3</sub>):  $\delta$  8.06 (1H, s), 6.92 (2H, d,  $J$  = 4.0 Hz), 6.74 (2H, d,  $J$  = 4.0 Hz), 4.00 (2H, br s), 3.68 (2H, br s), 3.50 (4H, br s). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  161.1, 141.6, 138.4, 125.4, 120.1, 120.0, 118.7, 115.5, 51.8, 50.7, 46.5, 40.8. LC-MS: RT: 1.93 min,  $m/z$ : 206.20 [M+H]<sup>+</sup> at 210 and 254 nm.

#### **4-(2-(Dimethylamino)phenyl)piperazine-1-carbaldehyde (33).<sup>(10)</sup>**

To a stirred solution of **32** (2.0 g, 9.75 mmol), zinc chloride (678 mg, 4.9 mmol), and 37% aqueous formaldehyde (3.693 mL, 48.75 mmol) in MeOH (10 mL) was added sodium cyanoborohydride (734 mg, 11.67 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 h. The reaction was quenched by addition of 1 M NaOH. The resultant mixture was extracted with ethyl acetate three times. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by flash chromatography on silica gel with EtOAc/heptane 4:1 to afford **38** (721 mg, 3.09 mmol, 32%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.08 (1H, s), 7.02–6.90 (3H, m), 6.86–6.83 (1H, m), 3.71 (2H, t,  $J$  = 5.0 Hz), 3.52 (2H, t,  $J$  = 5.0 Hz), 3.16–3.02 (4H, m), 2.83 (6H, s). R<sub>f</sub>: 0.3 (heptane/EtOAc 1:4).

#### ***N,N*-Dimethyl-2-(piperazine-1-yl)aniline (34).<sup>(10)</sup>**

To a solution of **33** (0.721 g, 3.09 mmol) in MeOH (10 mL) was added a 2 M solution of HCl in MeOH (10 mL), and the mixture was stirred at 50 °C for 1 h and concentrated. The residual solid was suspended in diethyl ether, filtrated, and vacuum-dried to give the desired product as a colourless solid. The crude product was used without further purification.

#### **Determination of Lipophilicities<sup>(11)</sup>**

Lipophilicities were determined using a Dionex Ultimate 3000 HPLC equipped with degasser, autosampler, column-oven and UV-detector. The eluent was 50:50 (v/v) 25 mM sodium phosphate-buffer (pH = 7.4) and MeOH. Injected volumes were 100  $\mu$ L with a flow rate of 2 mL/min. The column was a Zorbax SB-C8 (250 mm  $\times$  4.6 mm, 5  $\mu$ m). The column oven was kept at 37 °C and UV detection was carried out at 254 nm. The logarithm of retention factor of reference compounds (phenol, acetophenone, *p*-cresol, benzene, toluene, chlorobenzene, benzophenone, naphthalene, diphenyl and phenanthrene) and tested compounds was calculated, and a plot of the reference values against their known logD values was used to extrapolate logD values for tested compounds.



## Binding assays

**Primary binding assays** were provided by the commercial supplier Cerep. Further information about the assay is given on Cerep's website [www.cerep.com](http://www.cerep.com).

	Compounds			
	14		10	
	% inhibition 10 <sup>-7</sup> M    10 <sup>-5</sup> M		% inhibition 10 <sup>-7</sup> M    10 <sup>-5</sup> M	
5-HT transporter (h) (antagonist radioligand)	28	<b>92</b>	<b>64</b>	<b>97</b>
5-HT <sub>1A</sub> (h) (agonist radioligand)	<b>61</b>	<b>99</b>	15	<b>93</b>
5-HT <sub>1B</sub> (antagonist radioligand)	-7	36	-9	<b>62</b>
5-HT <sub>1D</sub> (agonist radioligand)	17	<b>77</b>	12	<b>59</b>
5-HT <sub>2A</sub> (h) (antagonist radioligand)	44	<b>99</b>	<b>86</b>	<b>100</b>
5-HT <sub>2B</sub> (h) (agonist radioligand)	33	<b>98</b>	44	<b>97</b>
5-HT <sub>2C</sub> (h) (antagonist radioligand)	-13	<b>78</b>	-7	<b>80</b>
5-HT <sub>3</sub> (h) (antagonist radioligand)	-3	-8	-11	-1
A <sub>1</sub> (h) (antagonist radioligand)	2	-9	-21	-13
A <sub>2A</sub> (h) (agonist radioligand)	-3	-6	9	8
α <sub>1</sub> (non-selective) (antagonist radioligand)	<b>55</b>	<b>97</b>	<b>58</b>	<b>98</b>
α <sub>2</sub> (non-selective) (antagonist radioligand)	21	<b>95</b>	36	<b>98</b>
AMPA (agonist radioligand)	0	8	3	10
β <sub>1</sub> (h) (agonist radioligand)	6	40	1	43
β <sub>2</sub> (h) (agonist radioligand)	-1	<b>53</b>	1	26
Ca <sup>2+</sup> channel (L, diltiazem site) (benzothiazepines)	-9	<b>50</b>	-11	35
caspase-3 (h)	-1	3	0	2
D <sub>1</sub> (h) (antagonist radioligand)	15	<b>92</b>	39	<b>98</b>
D <sub>2S</sub> (h) (antagonist radioligand)	23	<b>93</b>	22	<b>89</b>
dopamine transporter (h) (antagonist radioligand)	-7	41	4	36
EGFR kinase (h)	11	8	18	15
ETA (h) (agonist radioligand)	5	0	-11	-18
GABA (non-selective) (agonist radioligand)	-6	-8	-1	-3
H <sub>1</sub> (h) (antagonist radioligand)	<b>73</b>	<b>97</b>	<b>80</b>	<b>98</b>
H <sub>2</sub> (h) (antagonist radioligand)	-5	49	-7	<b>69</b>
I <sub>1</sub> (agonist radioligand)	10	25	12	14
KATP channel (antagonist radioligand)	-1	6	4	6
KV channel (antagonist radioligand)	1	-2	-4	1
M (non-selective) (antagonist radioligand)	1	<b>61</b>	5	<b>70</b>
N neuronal α <sub>4</sub> β <sub>2</sub> (h) (agonist radioligand)	1	-10	-3	-7
Nav1.5 (automated patch-clamp)		23		45
NMDA (antagonist radioligand)	3	6	3	0
norepinephrine transporter (h) (antagonist radioligand)	1	12	-1	26
opioid (non-selective) (antagonist radioligand)	6	<b>74</b>	-19	<b>74</b>
PKCα (h)	-3	-8	-1	-3
sigma (non-selective) (h) (agonist radioligand)	<b>50</b>	<b>98</b>	<b>79</b>	<b>98</b>
Y (non-selective) (agonist radioligand)	-8	-7	-7	0

### **Radioligand Binding Assay and Data Analysis.**

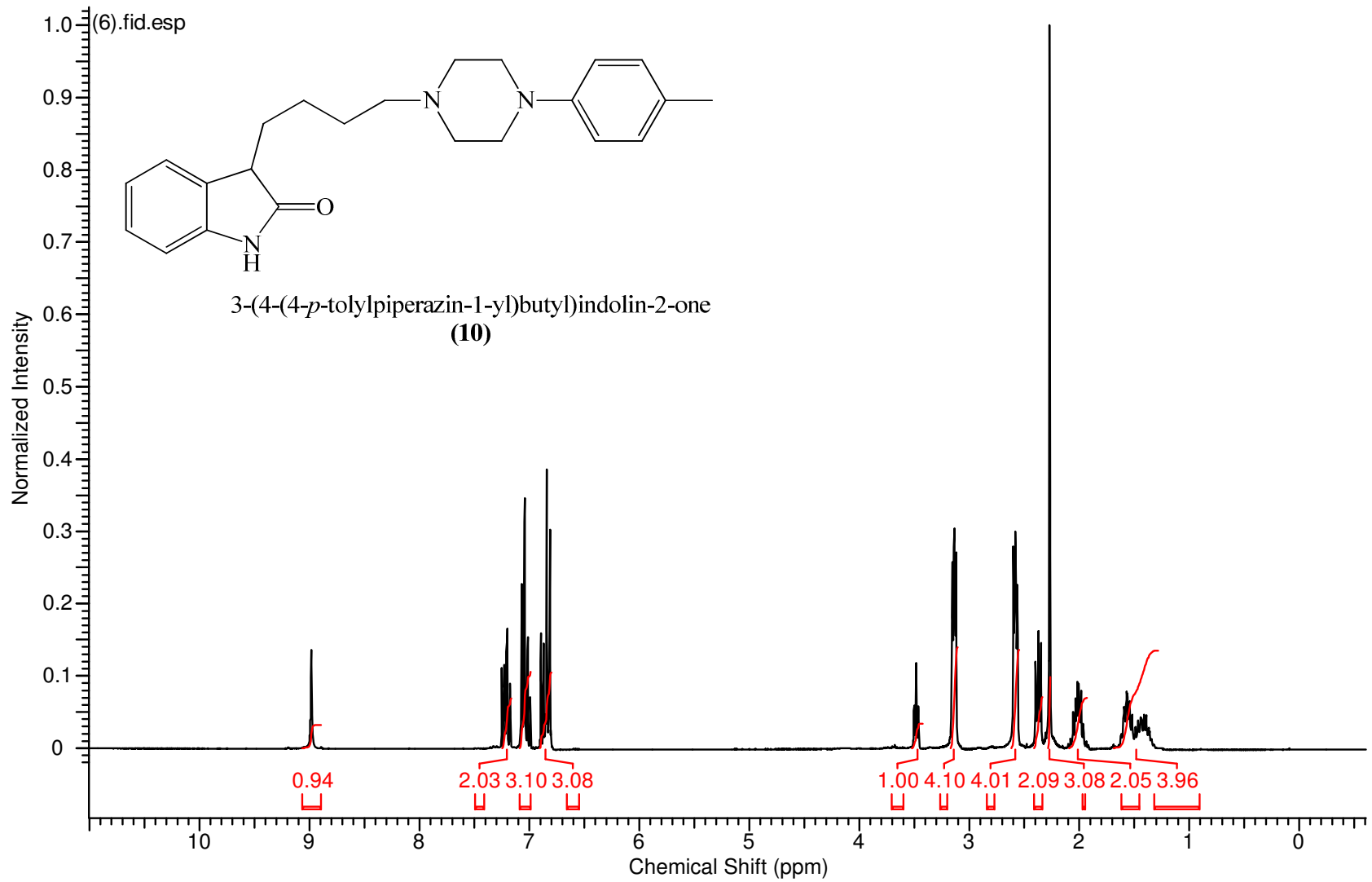
Subsequent to the initial screen,  $K_i$  values for compounds of interest were determined for 5-HT<sub>1A</sub>, 5-HT<sub>2A-C</sub>, 5-HT<sub>7A</sub> and adrenergic  $\alpha_1$  (ADR  $\alpha_1$ ) receptors in ligand binding assays, the conditions of which are briefly summarized in the Table 1. All assays were carried out at room temperature, the membranes were filtered over GF/C filters presoaked in 0.5% (w/v) polyethyleneimine to determine the bound fraction, and radioactivity was quantified by liquid scintillation counting in a Perkin-Elmer Top-Count device. Ligand-displacement curves (6 concentrations, 3 replicates) were fitted by non-linear regression using Graphpad Prism v. 5.0 and  $K_i$  values were calculated according to the Cheng-Prusoff equation.

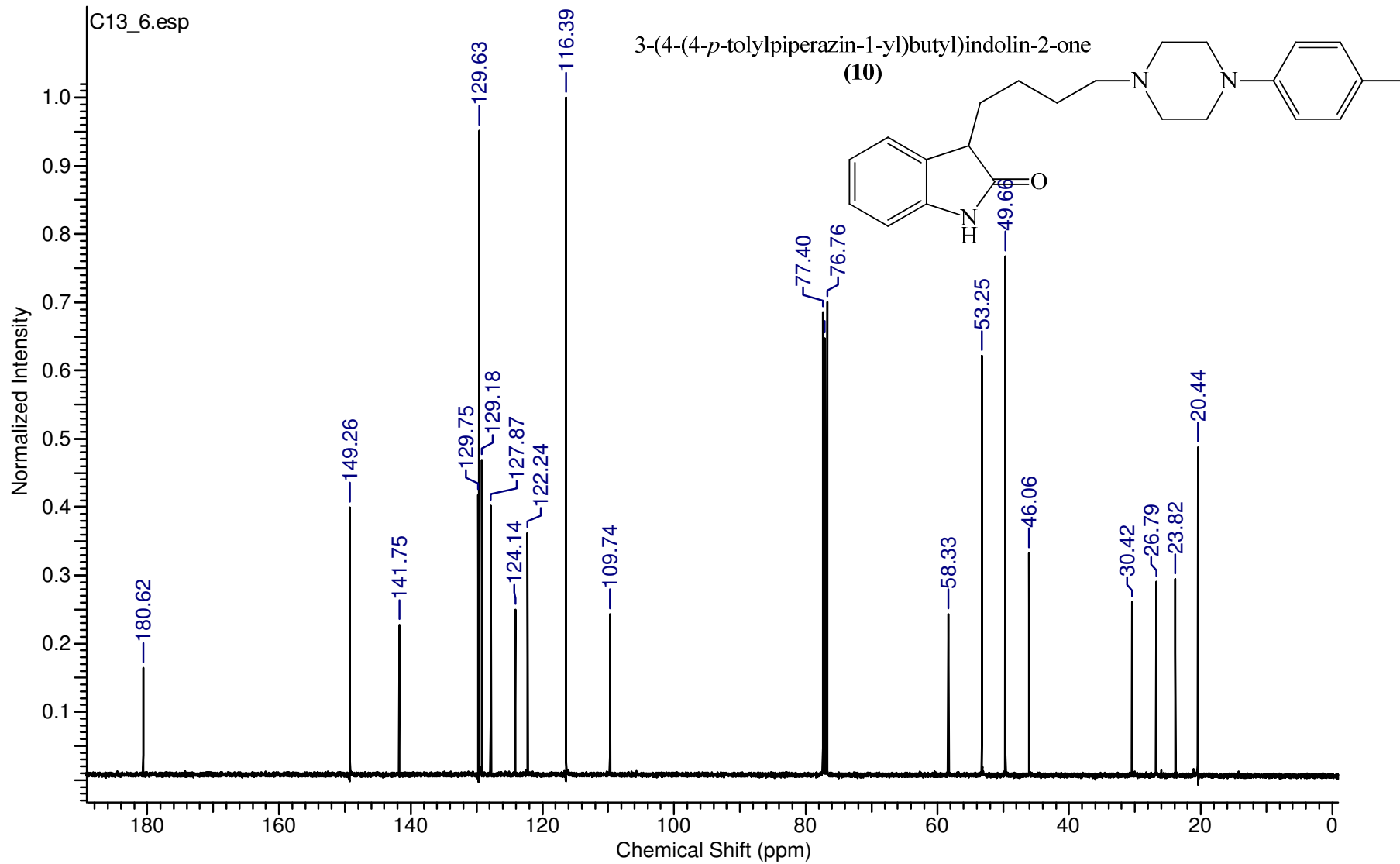
**TABLE 1**

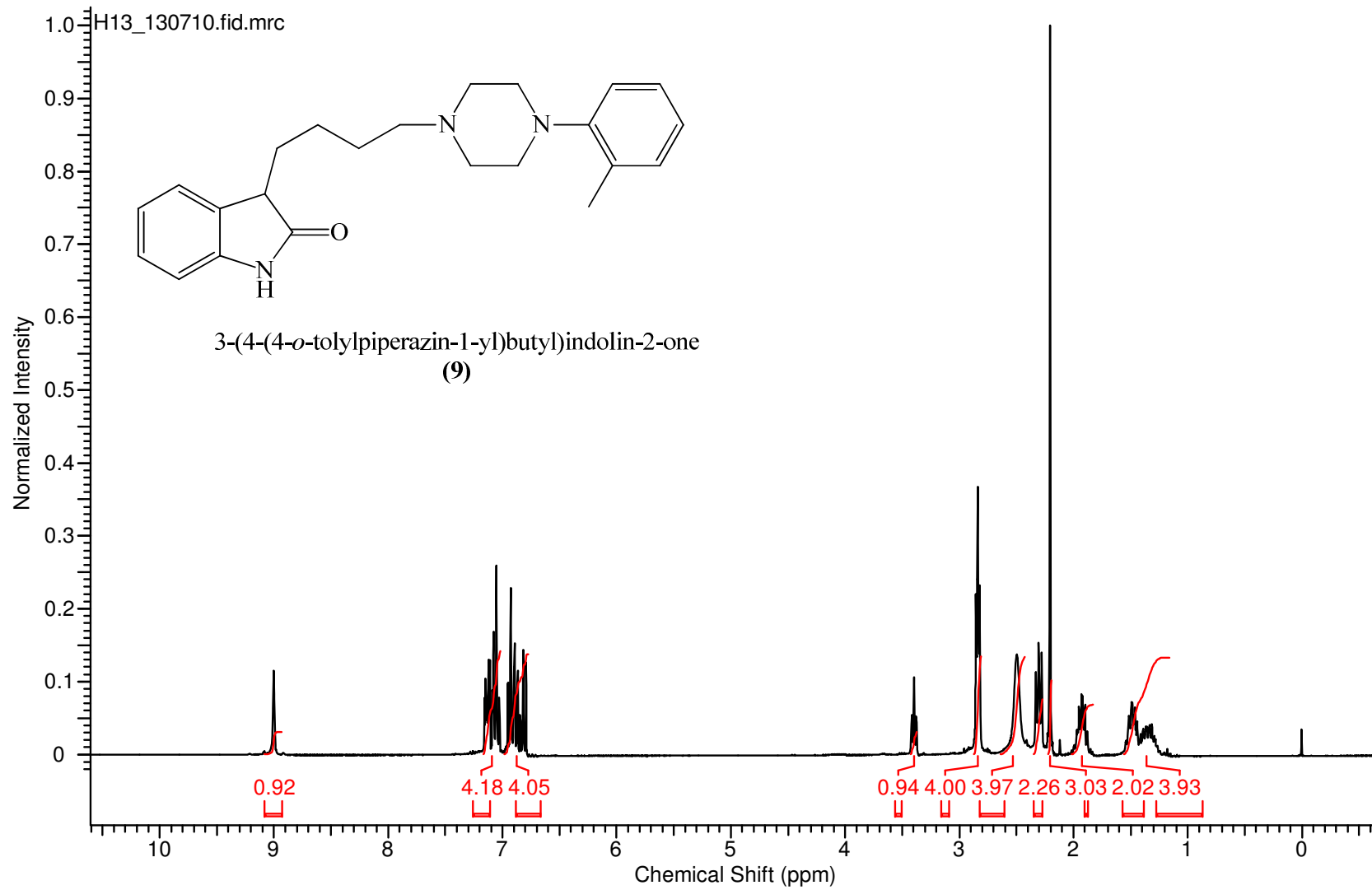
<b>Receptors</b>	<b>Source of membranes</b>	<b>Radiotracer</b>	<b>Non-specific binding</b>
<b>5-HT<sub>1A</sub></b>	Hum. recomb CHO	[ <sup>3</sup> H] 8-OH-DPAT	10 $\mu$ M 5-HT
<b>5-HT<sub>2A</sub></b>	PerkinElmer ES-313-M400UA	[ <sup>3</sup> H] ketanserine	1 $\mu$ M mianserine
<b>5-HT<sub>2B</sub></b>	PerkinElmer ES-314-M400UA	[ <sup>3</sup> H] mesulergine	1 $\mu$ M mianserine
<b>5-HT<sub>2C</sub></b>	PerkinElmer ES-315-M400UA	[ <sup>3</sup> H] mesulergine	100 $\mu$ M mianserine
<b>5-HT<sub>7A</sub></b>	Hum. recomb HEK293	[ <sup>3</sup> H] LSD	10 $\mu$ M 5-HT
<b>ADR<math>\alpha_1</math></b>	Rat cortex	[ <sup>3</sup> H] prazosine	1 $\mu$ M prazosine

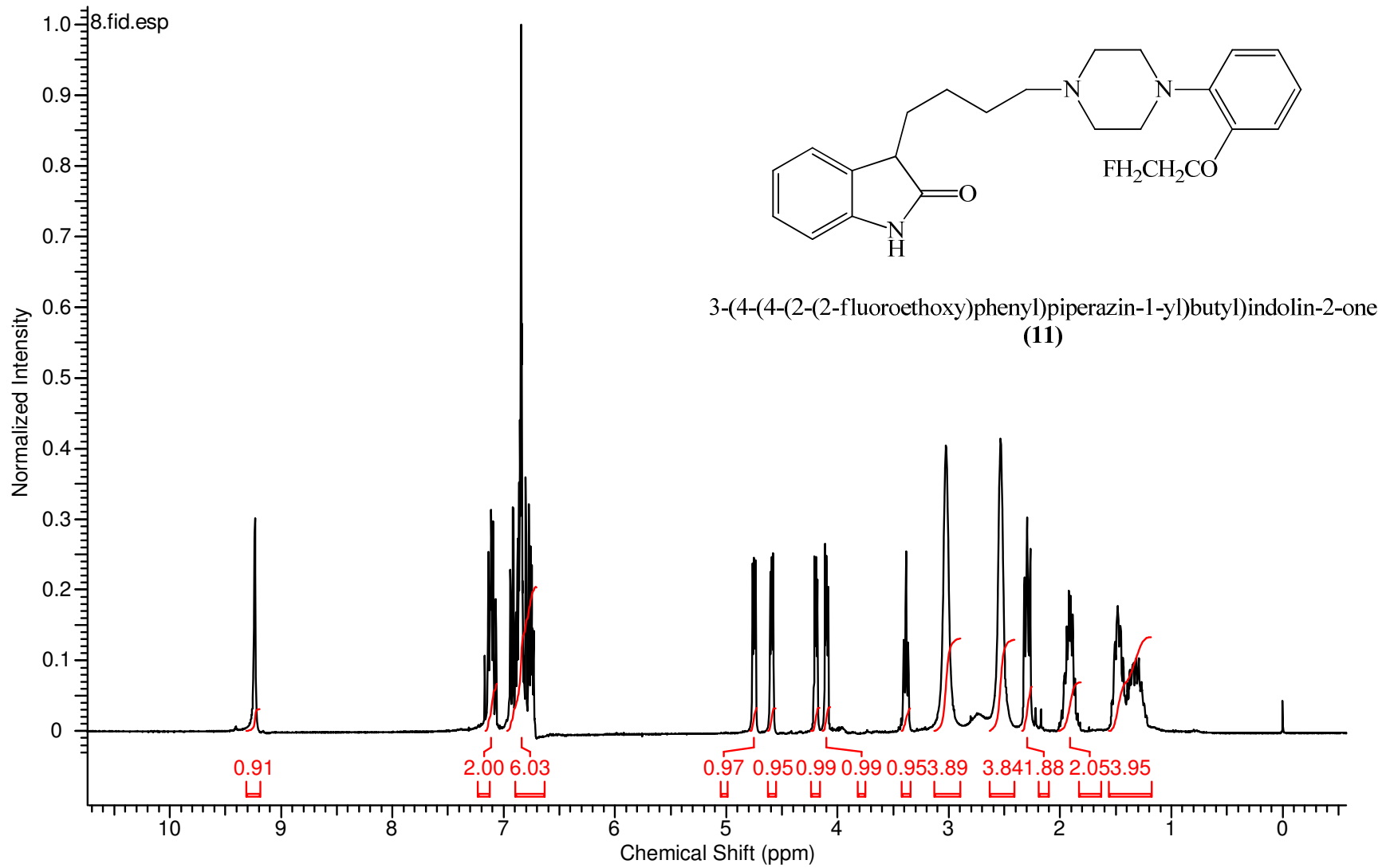
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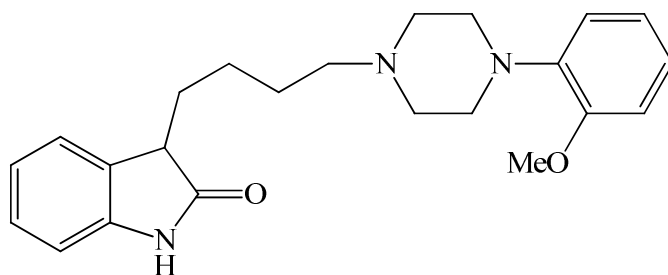




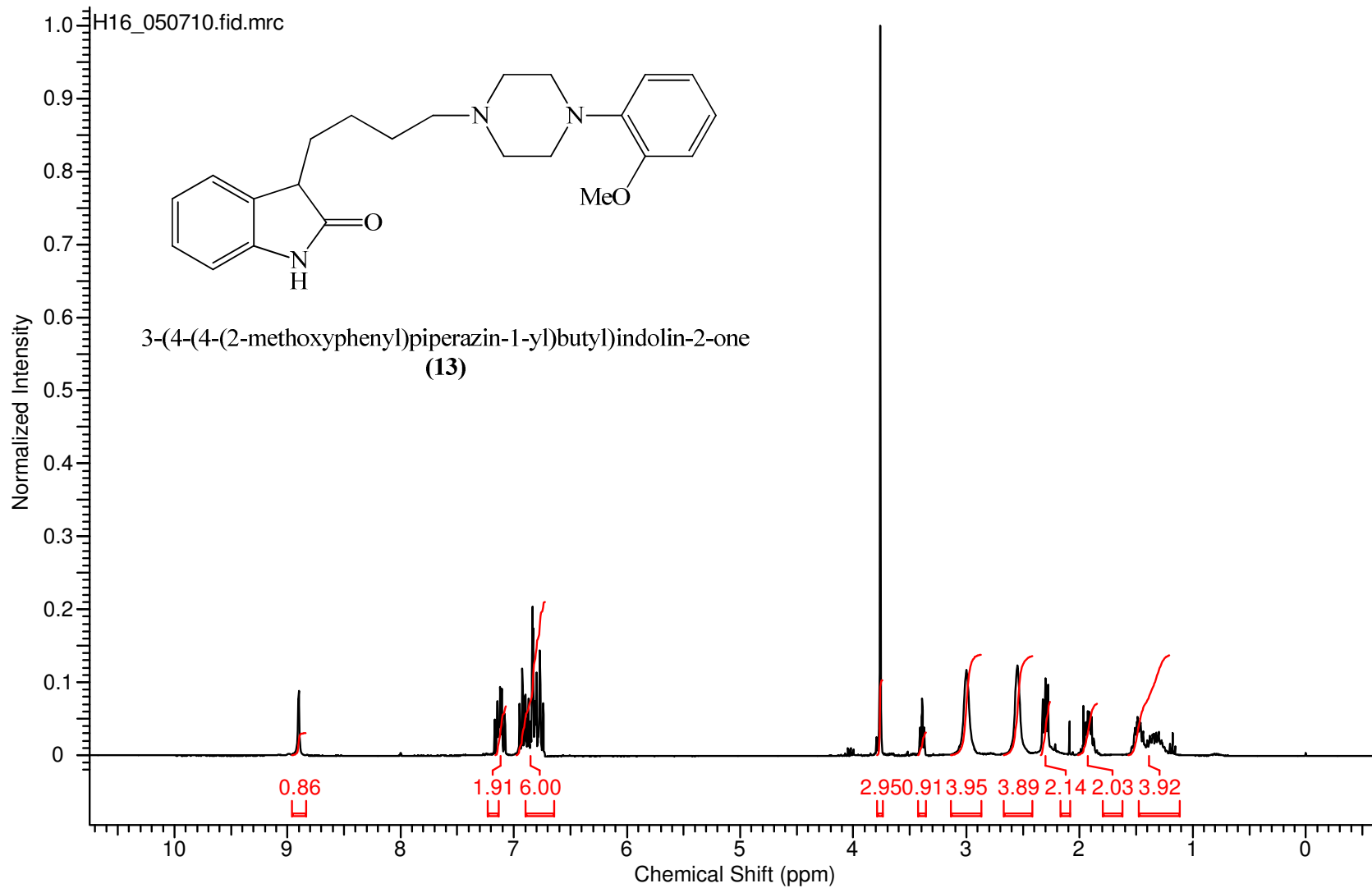




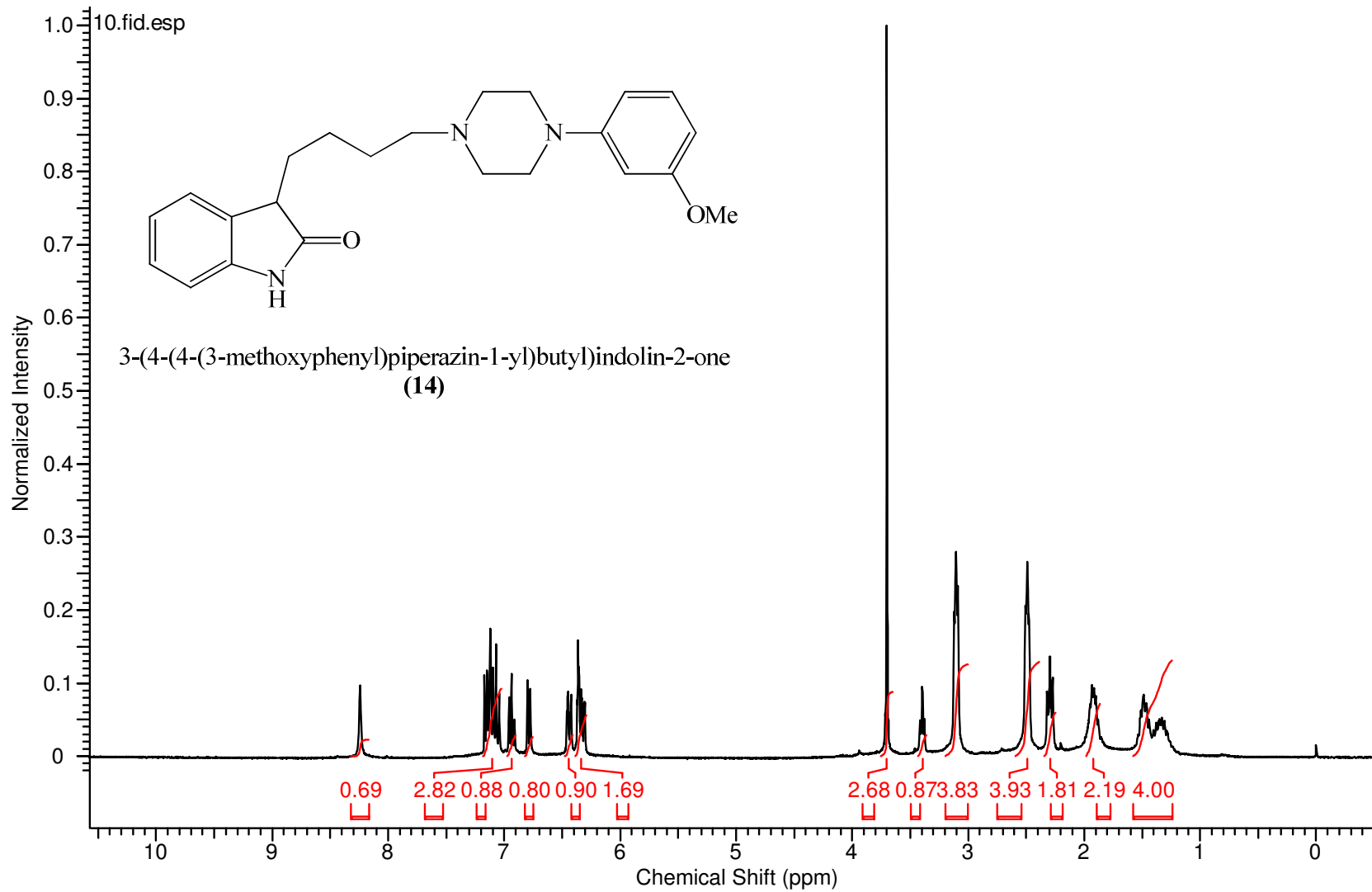
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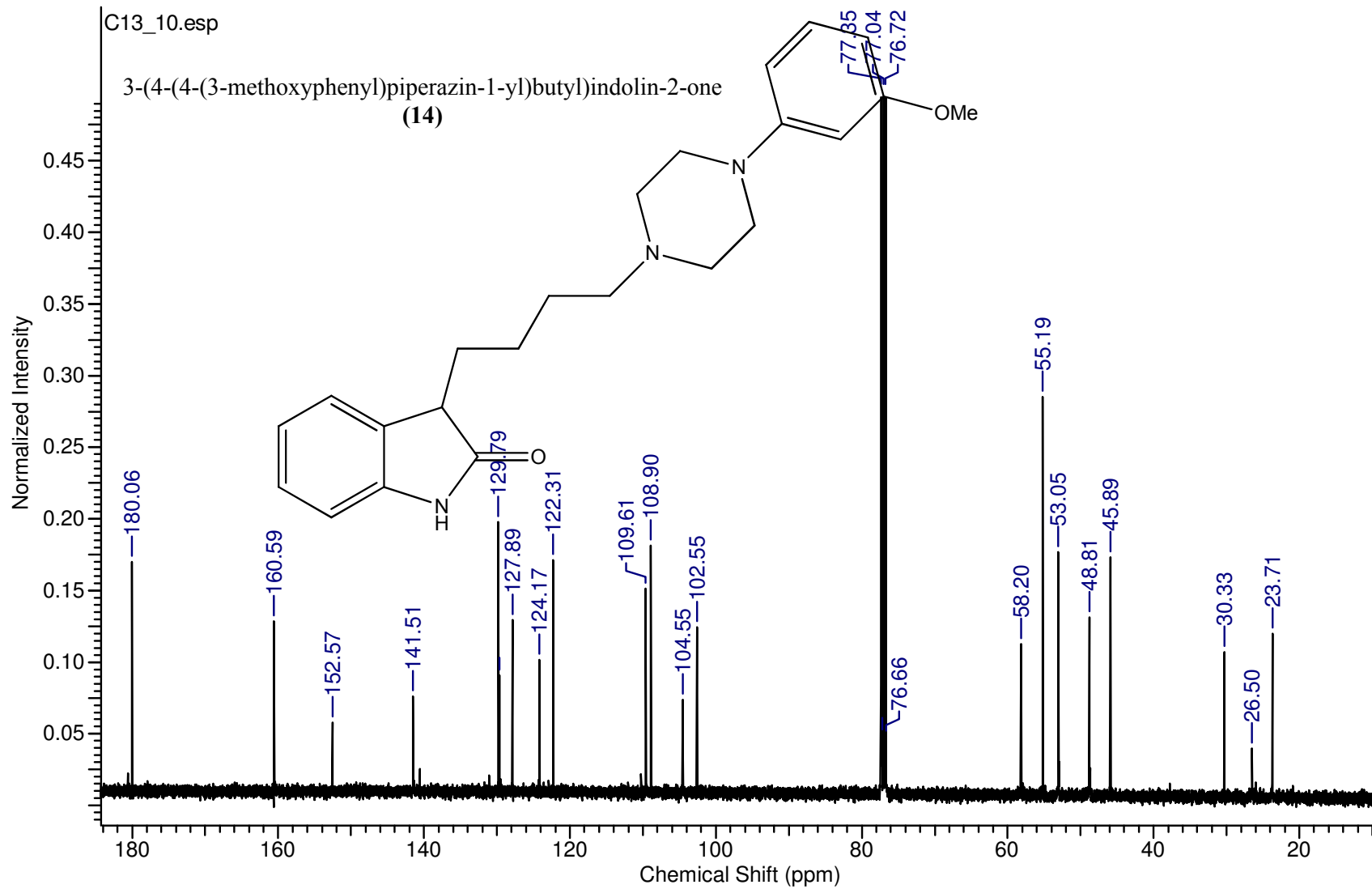


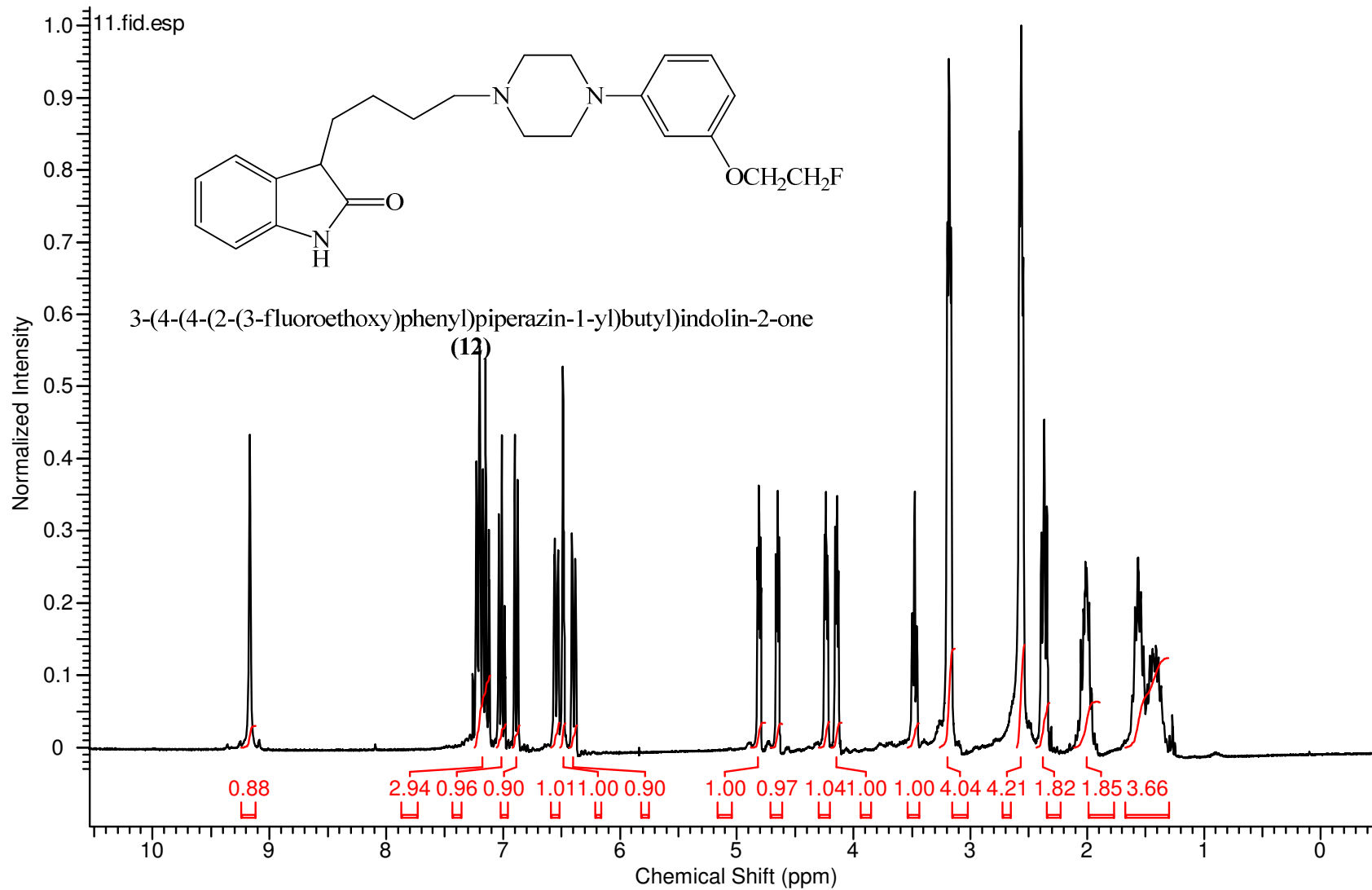
3-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)indolin-2-one  
(13)

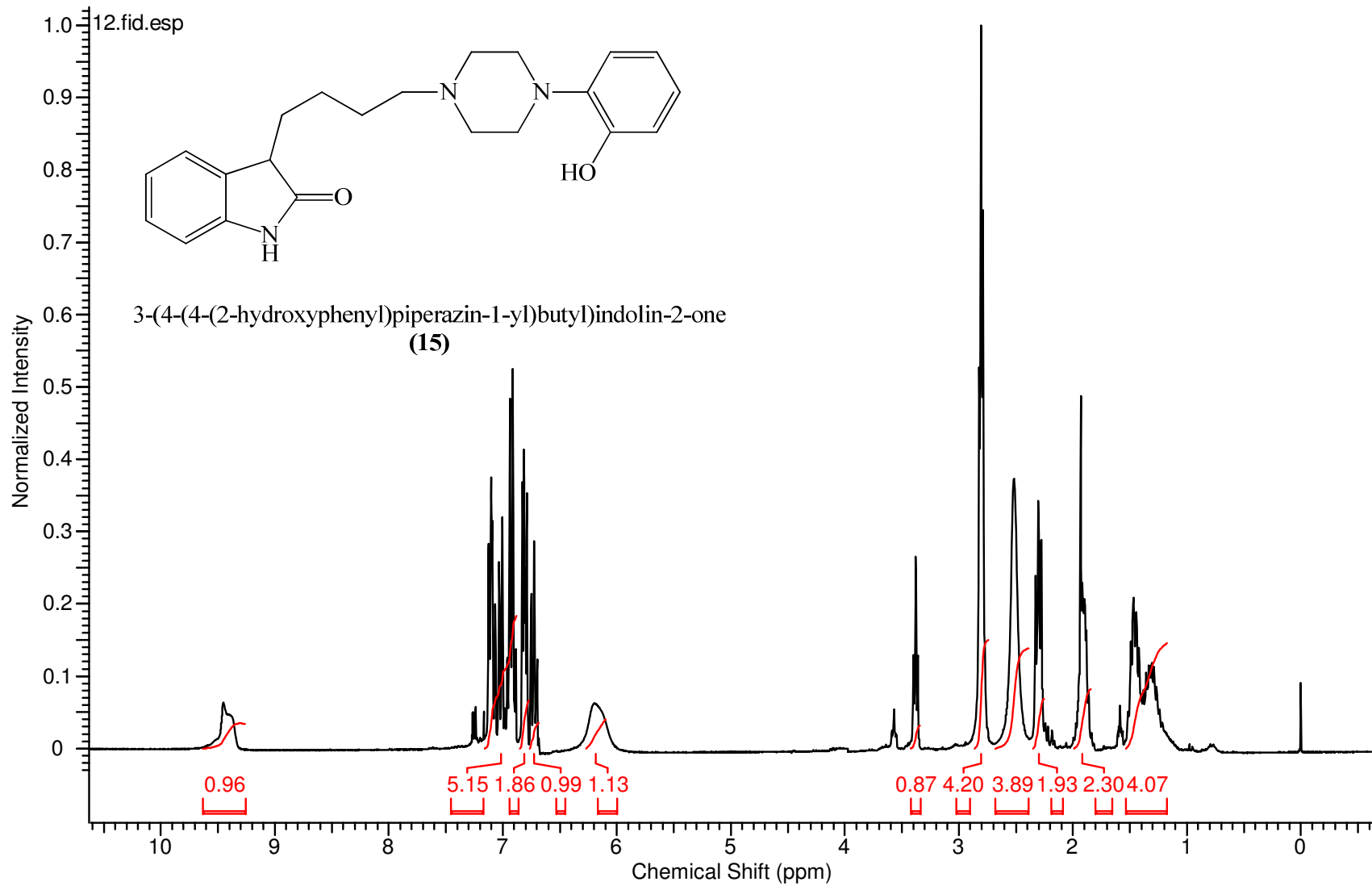


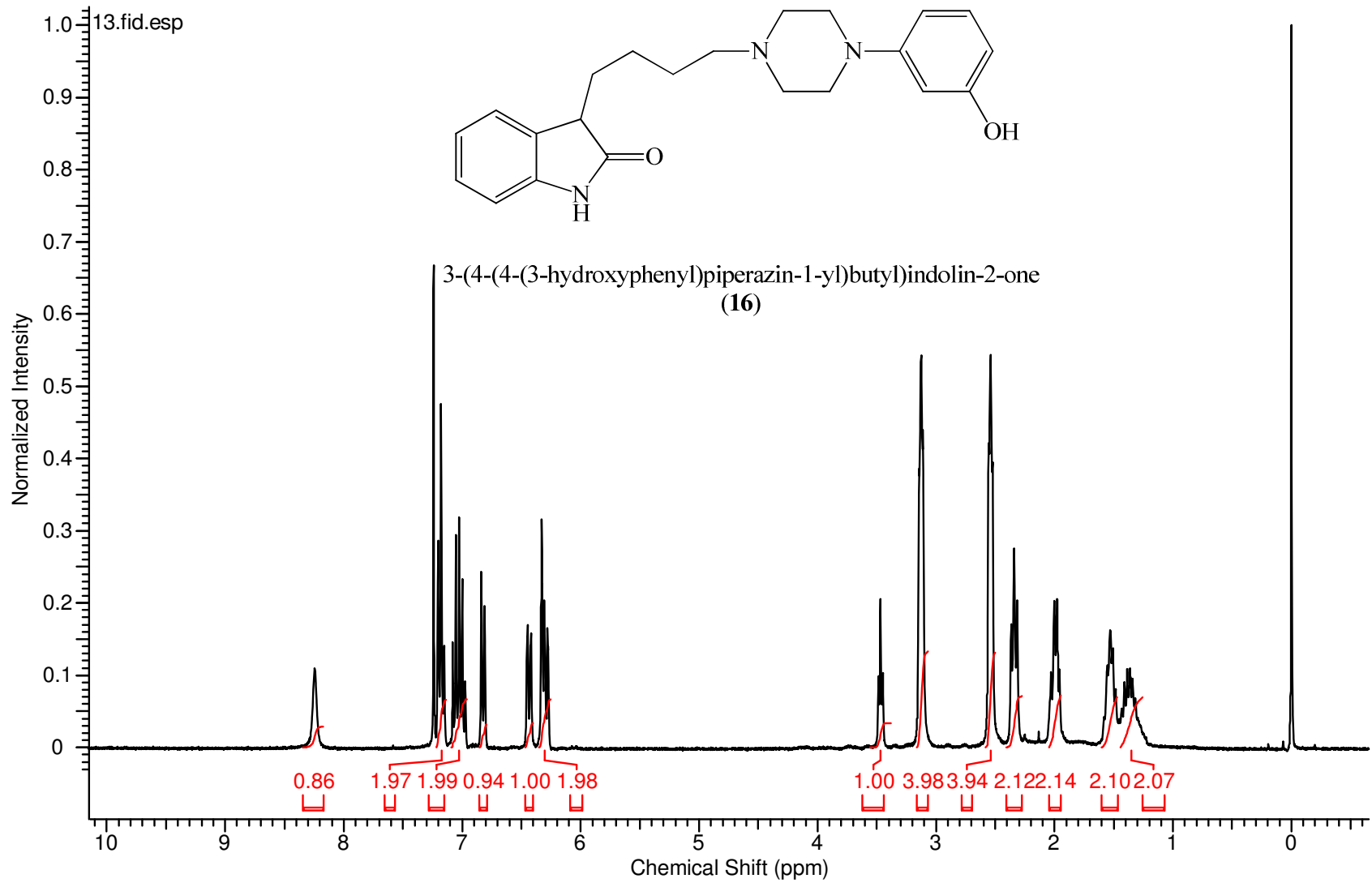


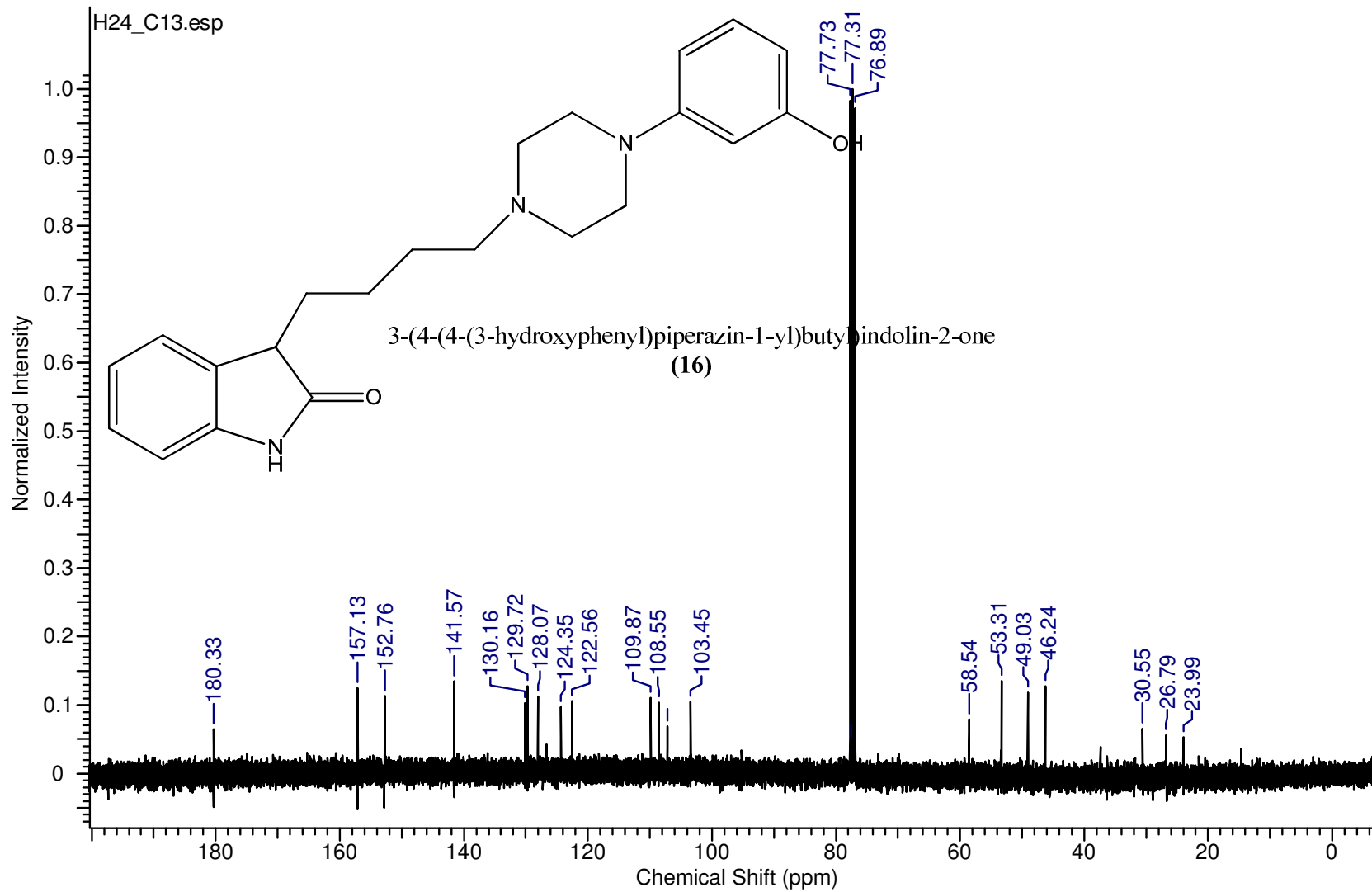


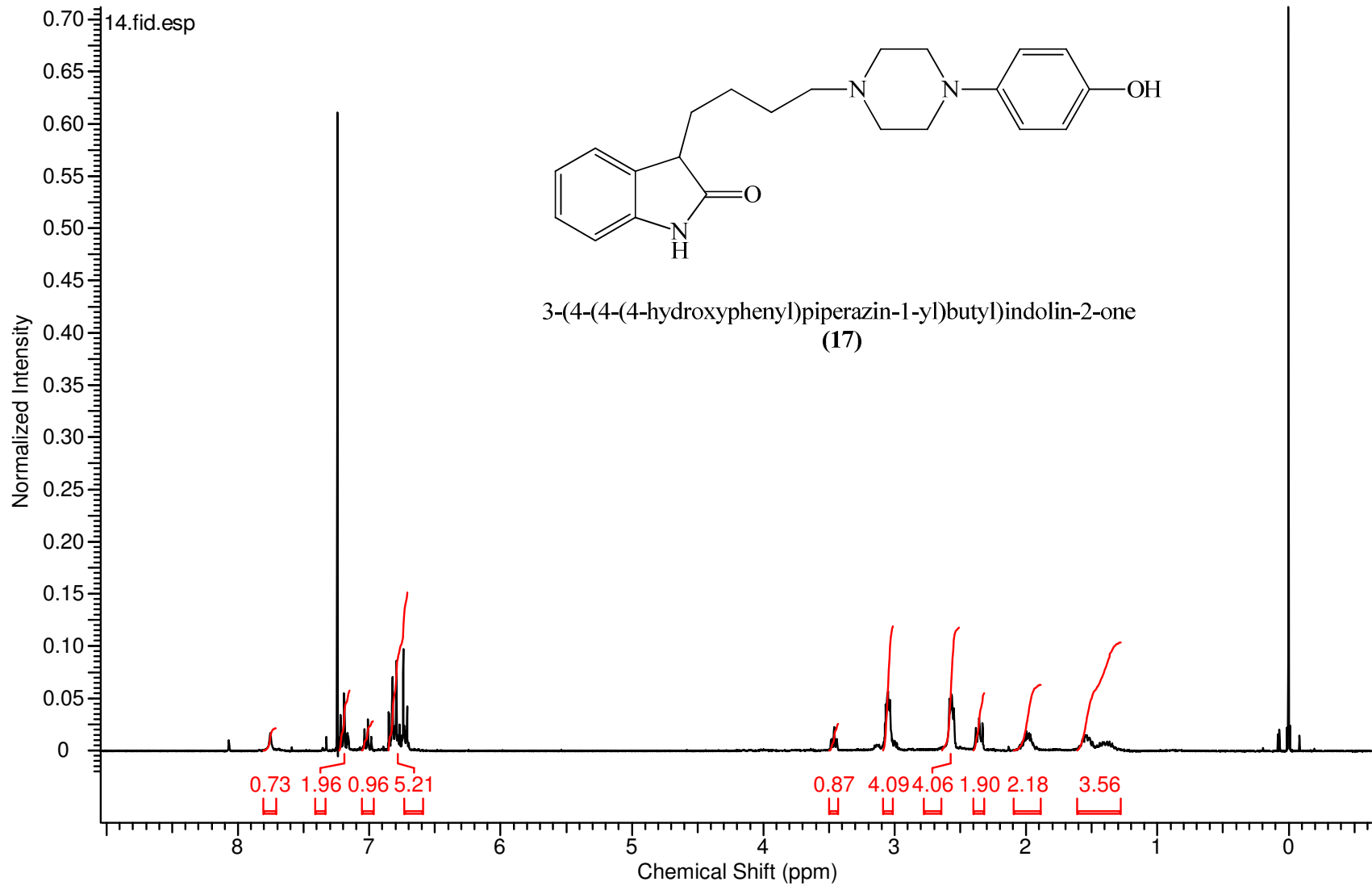


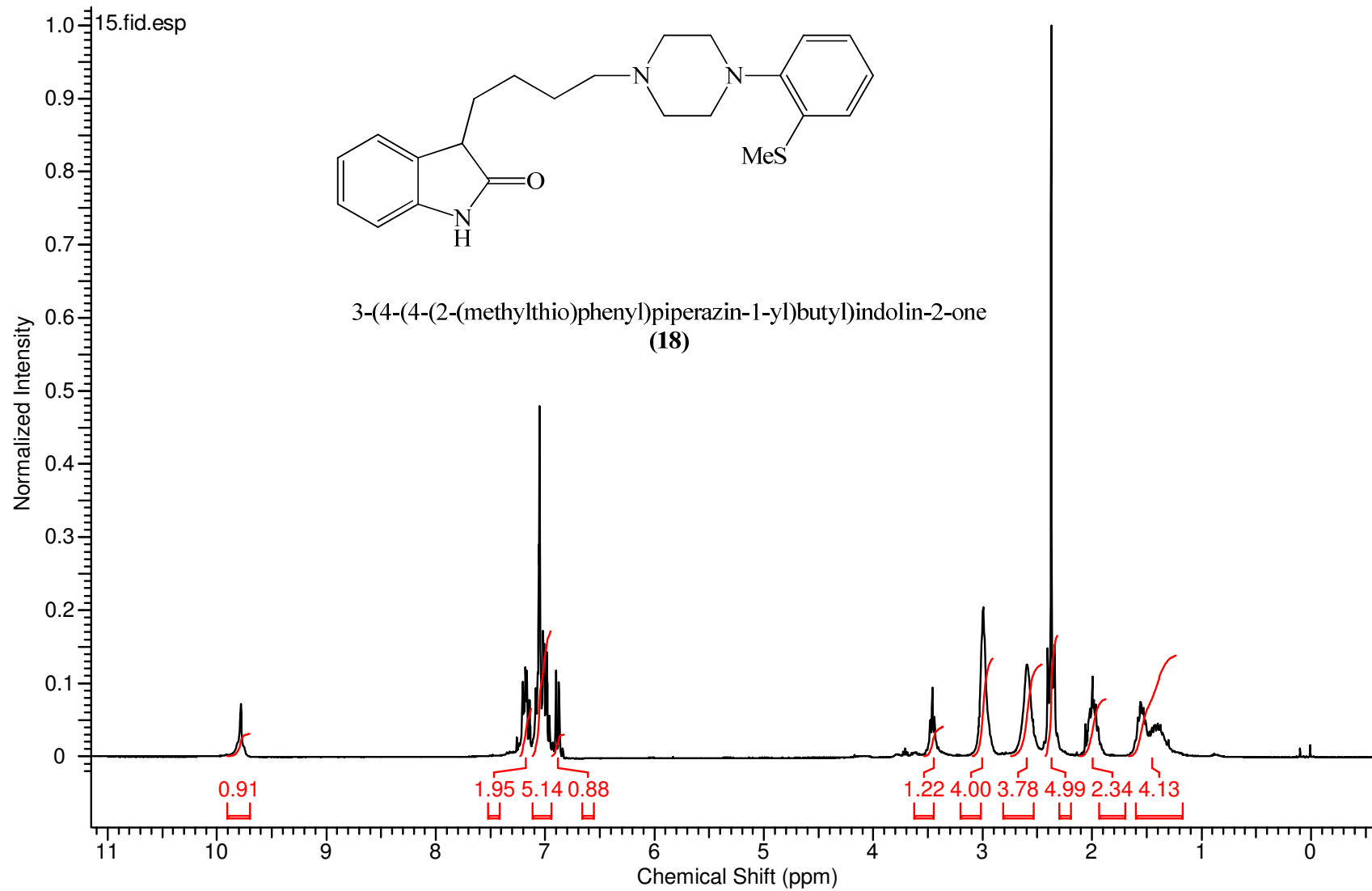




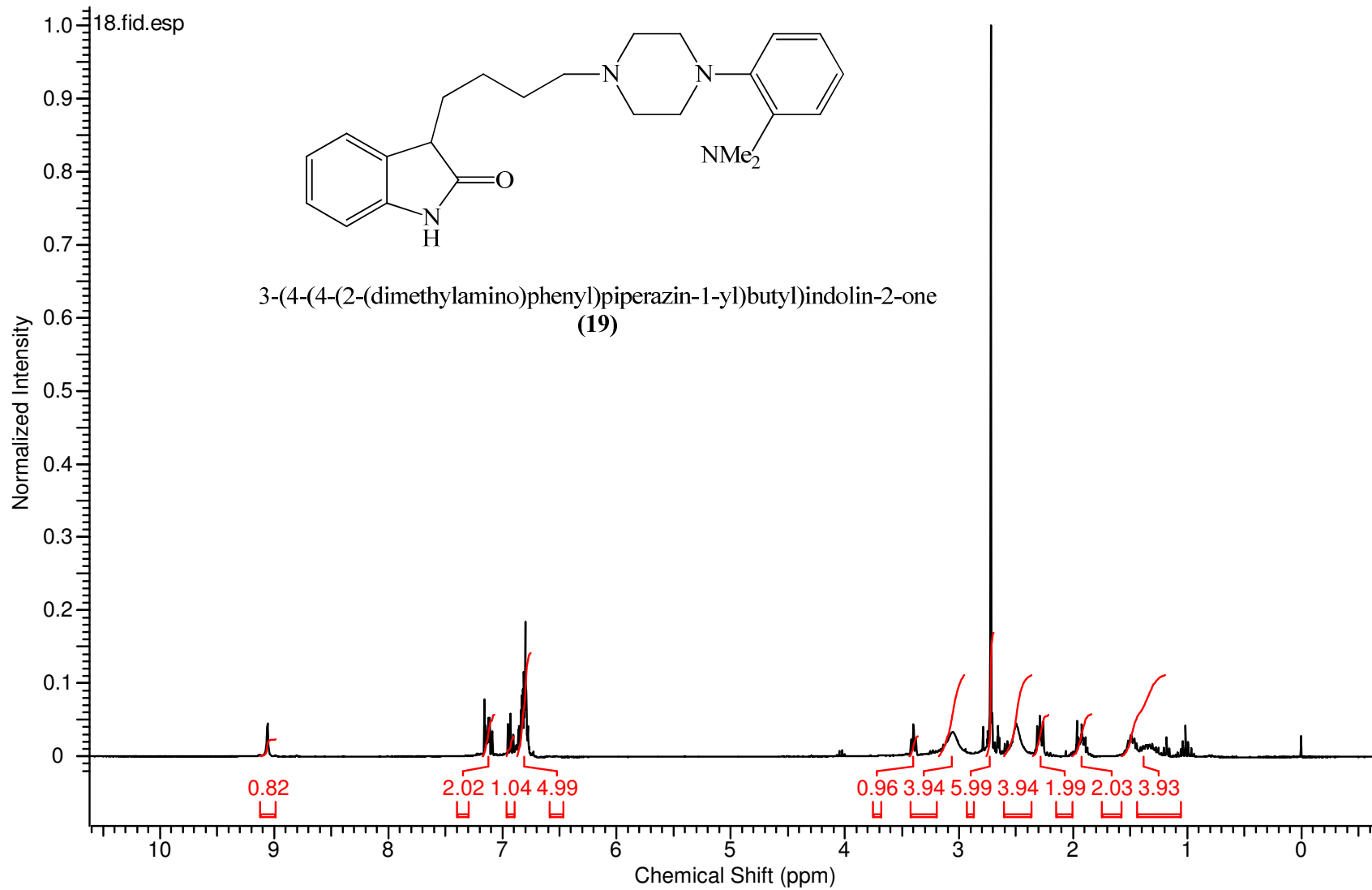


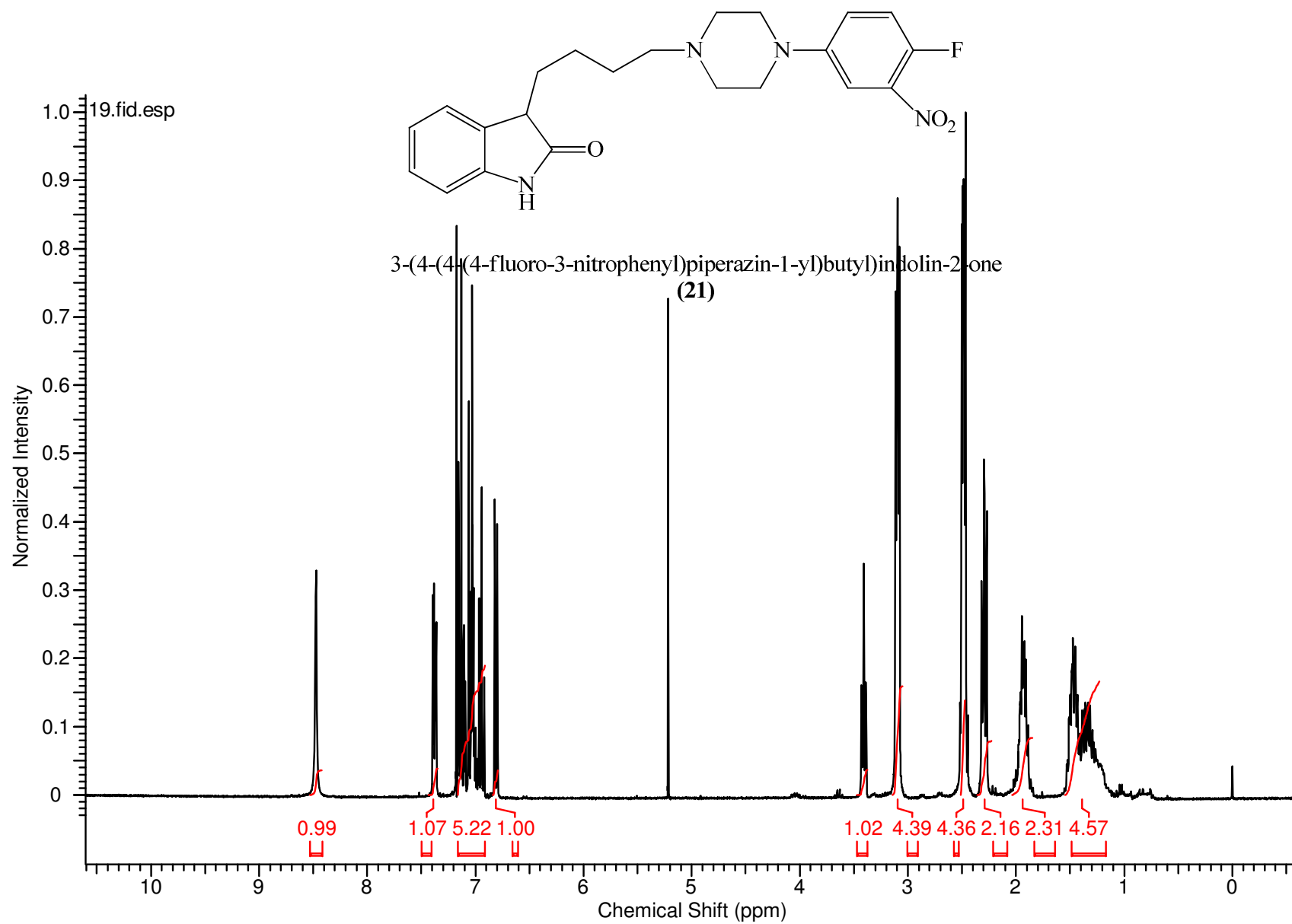


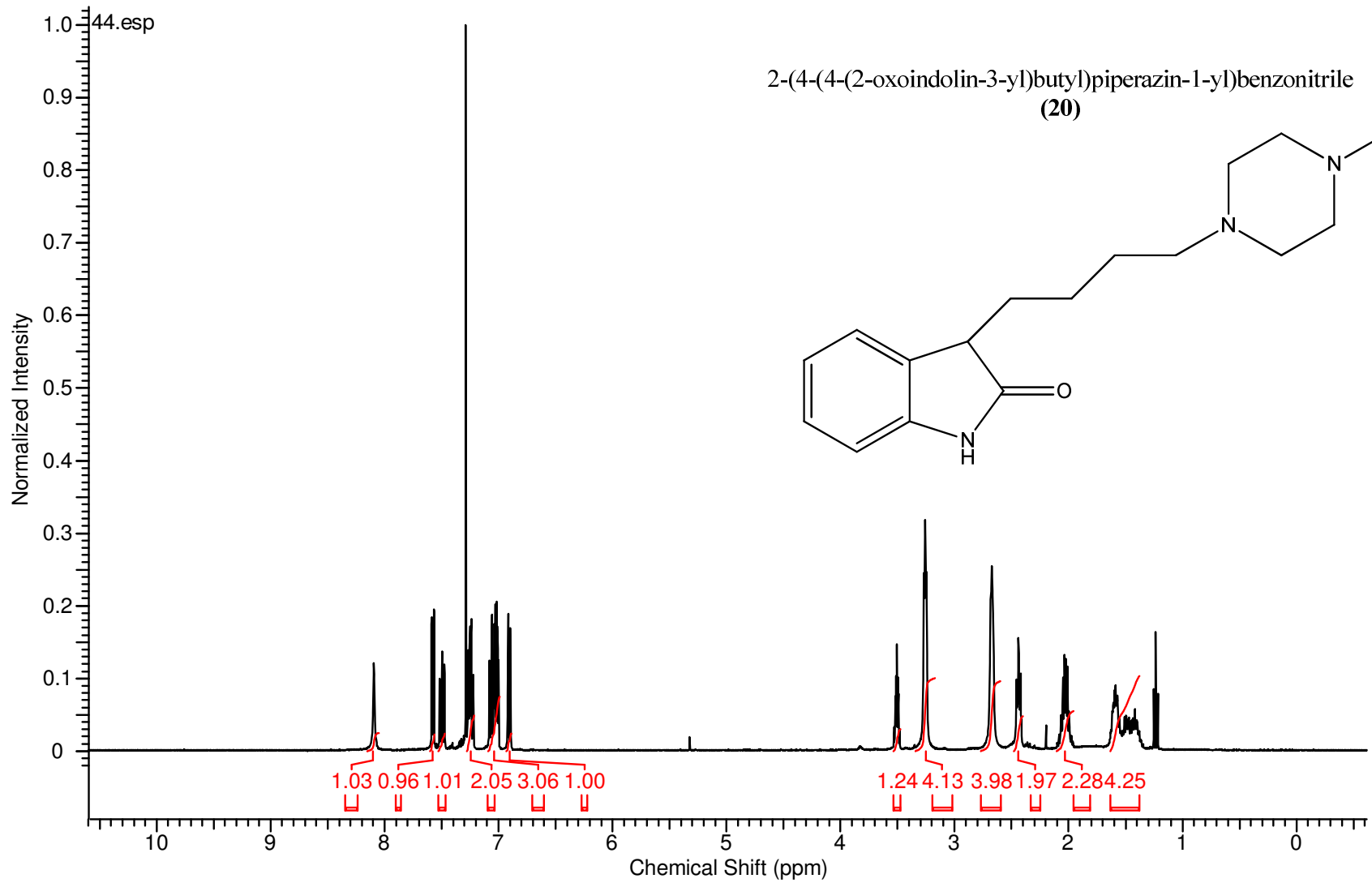












(4-chlorophenyl)piperazin-1-yl)butyl)-3-hydroxyindolin-2-one  
(23)

O=C1c2ccccc2N1CCC(CCCN3CCN(CC3)CCc4ccc(Cl)cc4)O